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THE FUNCTION OF THE COLLEGE *

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I SHOULD like to devote the brief time available for a presidential address to a further consideration of certain questions which I put before you at the dinner last year in St. Louis, and which are also closely related to some of the problems raised by Dr. Miller in his excellent Presidential Address in Detroit, the year before that.

The first of these concerns why we call ourselves a College of Physicians. Is there any special significance in the fact that we have selected the appellation College rather than that of Society or Association? What, after all, is a college in the sense in which we have used the word and what is its proper function?

We need not trace the evolution of the term from Roman days to our own. We may note, however, in passing that for the most part it has, one way or another, usually been connected with affairs of the intellect, with the efforts of man to improve his mind.

In America, colleges have been the forerunners of universities. In England, the old universities are made up of many colleges. These are both social and educational units. In Great Britain there are also the professional colleges, the Royal Colleges of Medicine and Surgery.

These last, since they are in some measure the prototypes of our own College, are worthy of scrutiny. King Henry the VIIIth, in granting a charter to the Royal College of Physicians of London, said "his main reason was to check men who professed physic rather from avarice than in good faith, to the damage of credulous people; accordingly, after the example of other nations, he had determined to found a college of the learned men who practised physic in London, in the hope that ignorant and rash practitioners might be restrained or punished." (British Med. Jr., April 3, 1915, p. 607.)

The English Royal Colleges, in addition to other functions, possess those of licensing boards. In 1913, Mr. R. J. Godlee, addressing the American

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College of Surgeons, at its foundation, on the "Origin and Growth of the Royal College of Surgeons of England" (*Lancet,* 2, 1913, p. 1443), remarked that "If you . . . desire that the diploma" F. A. C. S. "shall indicate, not only that a man can pass a severe examination, but that he has been thoroughly well trained, you will be well advised to lay down a special curriculum (I speak the word with dread) over and above that required in the ordinary university course, and to frame the examinations on a standard even higher than the highest degree examinations. It is, in my opinion, essential that the examination should be conducted independently of any medical school, and that the examiners should be chosen only from those who are actually engaged in teaching. It is also highly advisable that examiners should, whenever it is possible, be Fellows of your College and that no candidate should be examined by his own teacher."

Neither the American College of Surgeons nor the American College of Physicians can attain to this quasigovernmental status of the British Royal Colleges. They have no charters, royal or otherwise. They are self-appointed and possess constitutions drawn by their founders in place of charters. None the less, through the prestige which they are gaining, they may accomplish in the elevation of professional skill and learning, something akin to what the Royal Colleges accomplish through authority.

It is probably for the best in this country that minimum standards of professional qualifications be set and enforced by the state. It is for the profession voluntarily, through its various institutions, and by the efforts of its individual members, ever to strive far to exceed these minimum requirements. This is in accordance with sound American tradition. The various boards for certification in specialties, like that for internal medicine which is fostered by this College in collaboration with the American Medical Association, are examples of voluntary efforts for improvement in the quality of professional work.

The College, however, must be more than an instrument for raising standards of practice, if it is to deserve the name of College. To be worthy of such a name in truth it must become a breeding place of ideas, a nourisher of learning, a defender of intellectual freedom, a builder of professional morals, a forum in which can be expressed *any* honest opinion relating to the practice of physic in *any* of its aspects, with the assurance that such opinion will receive dispassionate and disinterested attention and study, and that it will be appraised judgmatically in the light of experience. Should the College be merely another medical society, then it is in fact, not a college at all in the highest meaning of the term.

Let us consider for a moment our national medical association and the relation of this College to it. "Organized medicine," the Association has called itself; "the doctors' trust," it has been called by members of the laity; an institution, be it said at once, which has accomplished great good, but one which by reason of its political nature is subject to certain limitations by which, on the contrary, a College such as this one of ours, is not bound. I

apply the term political to the American Medical Association advisedly. I use it descriptively, not critically. Its organization is patterned somewhat after the political structure of the United States. Its relation to state societies is roughly analogous to that of the federal government to the states themselves. The behavior of the Association is political. It is partisan behavior; it champions a cause. At the present time the cause is something close to standpatism. But the policy can be changed at any time, if the membership wills it, just as can that of the federal government, if the citizenry wills it. At the present time the electorate of the American Medical Association is apathetic and inarticulate because it has no issues, no platforms set up to vote for. It is allowing the medical politicians to run things about as they please, and official spokesmen, like Jove on high Olympus, to hurl their thunderbolts of wrath at all who differ with orthodox doctrine. As no democracy can be healthy without freedom of speech, real issues and an effective opposition party, it is desirable that those who believe in popular government bestir themselves to change this state of affairs. The British recognize this need so thoroughly that in Parliament, I am told, they speak of His Majesty's Loyal Opposition.

It is not my intention to devote this address to a critique of the American Medical Association. I have said what I have said in order to indicate what I conceive to be the fundamental difference between a college of physicians and a national or state medical society. Each has its use, but they are different. The college is not in competition with the medical association. The college should be the counterpart of the university, not that of the state. It is only through general elevation of the cultural level of society that a democracy can rise above mediocrity. The germinative centers of culture are the universities. This has been so since antiquity. They are the noblest institutions of man. They stand for no ulterior purpose. They are free as no other institutions are free. They are committed to no fixed policies other than that of acquiring and disseminating wisdom. It should be as unthinkable for us to have a College policy regarding social, economic, political or scientific aspects of medicine as for one of our universities to take sides in a political campaign. It should also be unthinkable that we should at any time be unwilling to hear all sides of any problem related to the practice of medicine.

We are in great need, as was made clear by Dr. Miller in Detroit, of medical statesmen, men of intellectual honesty, breadth of vision, courage, nobility of purpose and the qualities of leadership, who can find the way to the solution of some of the problems of medical service which now baffle both the profession and the public. The development of enlightened opposition within the democracy of the national association is one way of bringing to light such leaders; the development of a university atmosphere in a College such as this, is another.

The behavior of the College must be that of scholars. The College must not seek through propaganda to reach veiled objectives, but rather it must

search for, and broadcast, the whole truth, insofar as it can ascertain it, in all matters relating to the work of the physician. It must set for the profession at large an example of fine professional character. These are its proper functions. It is as desirable that its membership include men of thoroughly diverse opinion as it is that university faculties should do so. We want no society of "yes-men," we want genuine thinkers; and if we have genuine thinkers, we are bound to have diversity of opinion, because, as a speaker, I recently heard, remarked, . . . "the only persons who think alike are those who do not think at all." In this connection, I should like to quote an editorial which appeared in 1933 in the *Lancet* (October 7, 1933, p. 812). "From the moment that the idea of any tests or qualifications for university teachers other than those of ability and intellectual honesty is entertained, decay must begin. . . . 'Cleverness, talent, skill, fluency, memory, all these are understood and rated in the market. A cultivated mind just because it is above all price is apt to be overlooked altogether.'" There is an idea here which this College may profitably make use of in selecting its members.

May I return to the American Board of Internal Medicine. This examining body which is the offspring of the College and of the American Medical Association requires that for certification as internists candidates must possess certain qualifications and must have had certain training.

The question arises at once then: Where are they to get this required training? Our sister College, the American College of Surgeons, has concerned itself with this question. Recognizing the internships and residencies of the United States, in a host of hospitals, taken collectively, as one great educational institution, it fancies itself, so far as the training of surgeons goes, as the coördinating, directing and administrative center. To use the somewhat imaginative language of the Chairman of its Board of Regents, the hospitals of the country, which train residents in surgery, are part of the campus of the American College of Surgeons. This may be subjecting the term campus to considerable strain, but none the less the idea is made clear by this wording. The College of Surgeons visualizes itself as constituting, in coöperation with the hospitals, a great college for graduate training in surgery, a training which will make it possible for men to qualify for certification as surgeons by the Board of Surgery. The College of Surgeons, furthermore, has invited the College of Physicians to coöperate with it and to perform in medicine a similar function. To what extent or in what way it is wise for us to do so has not been determined. It is a problem in which the part of wisdom is to proceed carefully. Certainly it is true that whereas the universities of the country have provided well for undergraduate teaching and for medical research, for graduate teaching they have done relatively little. Under these circumstances, there is an opportunity for the Colleges; that of Physicians as well as that of Surgeons, coöperating possibly with hospitals—far better I think with medical schools—to arrange for the continuation of professional training to the highest levels attainable.

The requirements for membership in the College are related to these matters. When the American Board of Internal Medicine successfully establishes itself as the generally accepted agency for certifying internists, then it will be logical for this College to make certification by it, or by an equivalent board in one of the other medical specialties, a prerequisite of membership.

Some of you may recall that at the Boston meeting in 1929, Dr. George Vincent told us we were an élite—a self appointed one at that. He said further that everyone wishes to become a member of an élite. If he cannot get into an existing one, he starts a new one, and after he has got all his friends in, he raises the entrance requirements. He intimated that that is what we have done. The jest is not devoid of application, but this need not depress us. So long as we do it for a high purpose, it is neither dishonest nor hypocritical for us steadily to raise our entrance requirements, even to a point where some of those of us already in could not pass were we to seek to enter now. The significance and usefulness of the College in the intellectual world of our profession will be determined entirely by the mental calibre, the moral fibre and the learning of its members. Anything we can do to elevate these is justifiable; anything we can do to promote the growth of medical scholarship is meritorious. The physician must continue to study throughout his life. The College must be made an instrument to help him do so.

Let us consider for a few moments what may be a proper scope for the deliberations and discussions of the College at its Annual Sessions, its regional meetings, through the medium of its journal, and the informal intercourse among its members. We were told in St. Louis that the doctor should stick to his last; a metaphor intended to mean apparently that we shouldn't bother our heads about anything but the scientific aspects of medicine. The social, economic, political, and even the philosophic aspects are none of our business. I hardly think it is necessary to seek arguments to refute this pronunciamento. It is palpably as ill balanced as is its opposite which we sometimes hear, that no one but the doctor should have any say in the regulation or method of dispensing medical practice.

The social, economic and political aspects of medicine certainly may rightfully engage the attention of a College of Physicians. That is why I have included, cautiously, a few such items in the present program. They also are of immediate concern to the public, the individual members of which —Johnnie Q., for example—may at any time become patients. Recently they have aroused the interest of both profession and laity to an unusual degree. They have given rise to a considerable amount of somewhat acrimonious discussion. That this should be so is altogether gratifying, for such discussions sometimes clear the atmosphere and thus permit a clearer view. Also there is the possibility that from them will emerge an idea or two, actually constructive.

I will not dwell longer on the social, economic or political aspects of

medicine. Instead, I should like to suggest briefly certain types of philosophical, or at least ethical, problems which I think might advantageously be included from time to time among the topics to be deliberated upon by the College: for example, the question of whose medicine is it? or does the patient exist for the doctor, or the doctor for the patient? The answer to this would seem simple, that the doctor exists for the patient, and yet when we get involved in problems of the provision of medical care, the conditions of medical practice, the methods of paying the doctor, the ethics get very complicated. The practice of medicine—is it a business or a profession? A profession, of course, you'll say, but what's the difference? The motive of business is profit. What is the motive of a profession? Profit also, but not profit alone. The professional man expects, and ought, to earn his living by practicing his profession. The physician wants, and is entitled to, adequate remuneration, but in addition he gets a part of his reward from the intellectual enjoyment which a calling requiring some learning bestows upon him (this reaches its highest pitch when he is able to make an original contribution to medical knowledge) and from the spiritual values which are to be derived from associating in a helpful way with many kinds of people. The profit element and the pleasure element both enter into the motivation of the physician. In considering his behavior and his relations to other classes in the community, it is best to face these facts realistically. It is idle to think of the physician as a consecrated sort of person giving himself idealistically to the cause of suffering humanity. Rarely he may be just that, as occasionally there are saints in other lines of human endeavor, but the rank and file of him are not, nor is it altogether desirable that they should be. If the laity wishes to idealize us, let it do so, but let us not be led from the truth of the situation thereby. As a matter of fact, the laity is more inclined nowadays to damn the doctor than to idealize him, and this is largely due to his inability to make his methods of dispensing medical service as efficient as a streamlined age requires. The layman, who may become a patient, is just as personally interested in the manner of provision of medical care as is the doctor, and I believe that any disinterested judge would say he had as good a right to be. The practice of medicine is the doctor's to make an honorable living by, and ideally to gain some happiness by; it is the layman's to have his health preserved by; the patient's to have his ills relieved by. When the interests of doctors and patients come into conflict, compromises must be reached through the display of fairmindedness on both sides.

We hear a great deal about the sacrosanct doctor-patient relationship. No third party can be allowed to come between the two involved. This has been used as an argument against all attempts to improve the efficiency of medical service through group practice. When it is suggested that a disinterested outside person could with greater equity than the doctor determine what might be a proper fee for services rendered in any given case, there are storms of protest from the conservative wing of the profession.

Yet a philosopher might recognize such an arrangement as an ideal one, and, as a matter of fact, it is actually working successfully in more than one place to the satisfaction of both doctors and patients. Professor Lawrence J. Henderson has considered the doctor and patient as a social system, analogous somewhat to a physico-chemical system, two elements acting upon one another through sentiments. The doctor must seek to influence the patient through the patient's sentiments, and he must take care not to let the patient's sentiments act upon him. In other words, he must keep his own sentiments out of the picture as much as possible. He must perform his professional duty disinterestedly, but if he is wondering all the time what sized fee the patient can pay him, or what sized fee it is fair for him to ask of the patient, how can he remain disinterested? I submit that having a third party determine the size of, and even collect the fee from the patient for the doctor, is not only not an intrusion into the holy doctor-patient relationship, but actually increases the likelihood of the patient's receiving from the doctor the best and wisest treatment the doctor is capable of giving.

Another thing that stimulates the doctor to do his best by his patient is to have his work overseen by his critical colleagues. If this is an intrusion into the holy relationship, then it is to the patient's best interest to have an intrusion. I do not believe that it can be successfully denied that the place where a patient is most likely to have his case diagnosed and treated correctly is in the public wards of a teaching clinic. This is not because the doctors are necessarily any wiser there, but because if one makes a mistake, another will observe and correct it. If one has some new information about diagnosis or treatment that applies to a given case, he will tell his colleagues about it. Why in former times did patients walk from Jerusalem to the Allgemeines Krankenhaus in Vienna? Because they knew that in that center of medical learning they stood the best chance of getting cured.

One other ethical question I should like to indicate. Is it noble or ignoble, is it wise or otherwise, that physicians and surgeons should give their professional services to the care of the indigent? There is also an economic question connected with this matter, but it is quite simple, namely, if doctors are to be paid for caring for the indigent, who is going to pay them? The answer to this is quite obvious. If they are to be paid at all it will have to be by the community because there is no other source. The ethical problem is more puzzling. By tradition, down through the ages, the physician has given his services to the poor. The fact that this has always been so, however, does not of necessity prove either the wisdom or the justice of the custom. Should the physician give his service to the indigent? Is he more obligated to see that the indigent get adequate care than is any other responsible member of the community? He possesses the skill to get them well perhaps, but should he be expected to give this away when other members of the community are making no parallel sacrifice? Of course, other members of the community will readily accept his gift so long as he is willing to make it. But why does he make it? Because it is traditional for him to

make it. Also because he gets a return for it, not in money, but in experience, in the prestige that attaches to a good hospital appointment (the indigent are cared for largely in hospitals), in the pleasure that is to be derived from associating with the other members of the staff of such an institution and, finally, in the spiritual uplift that is to be got from giving of one's self to the service of others.

Whether these rewards are adequate is a fit subject for discussion. Under ideal circumstances, as, for example, in privately endowed teaching clinics, undoubtedly they are. In large publicly supported hospitals, where the pressure of work is great and much of it is of a drudgery type, perhaps they are not. It must be admitted that if the profession should abandon its traditional custom of giving its service freely to the poor, something of an intangible or spiritual nature would be lost. However, we have to face the realities of our own day, and it is not unlikely that in many instances at least the indigent will get better medical service if the community pays for it.

It may be proper to add that even if the doctor is paid for caring for the indigent, he still has the opportunity to exercise his generosity, as does any other citizen, by giving of his substance to the most that he is able to the worthy causes of his community. Let him show the world that the doctor can be as good a citizen as any. Let him also, in rendering the service for which he is paid, add to it those qualities of spirit and purpose which cannot be bought with gold. Therein lies his chance to preserve the ancient values in the face of modern adaptations.

I must now draw this utterance to a close. I have sought to indicate to you my conception of a College of Physicians, of its nature and purpose, of its attitudes and of the scope of its deliberations and activities. In conclusion let me urge all members of the College, especially new members, to put, as members, scholarship first. Let me remind you that scholarship flourishes only in the atmosphere of freedom. There is indeed no place for "yes-men" in a truly learned society, nor is there place for political maneuvering, or reprisal for the expression of honest opinion. Recall the words of Voltaire, "Ecrassez l'infame." The infamy of which Voltaire spoke was religious bigotry. The bigotry of which we stand in dire peril today, as President Conant pointed out at the Harvard Tercentenary, is political bigotry. Let us strive, therefore, in this propaganda-poisoned world, to keep our land a free democracy and within it to make our College take on the essence and spirit of the university and thus become an instrument of service to humanity.

NEW EXPERIMENTAL DATA ON ARTIFICIAL HYPERTHERMIA *

By A. Bessemans, M.D., *Ghent, Belgium*

Giovanni Truffi recently reported that *Treponema pallidum* remains virulent when passed for one hour through the body of birds, which are supposed to have a body temperature of 42° C. (107.6° F.). Mario Truffi and Beck theorized on these results, and reached the bizarre conclusion that *Treponema pallidum* could resist, within the organism of birds, temperatures of 42° C. (107.6° F.) during at least five hours. They deduced from the experiments of Giovanni Truffi that mere thermic rise is not the cause of the action of malaria therapy and of pyretotherapy in general.

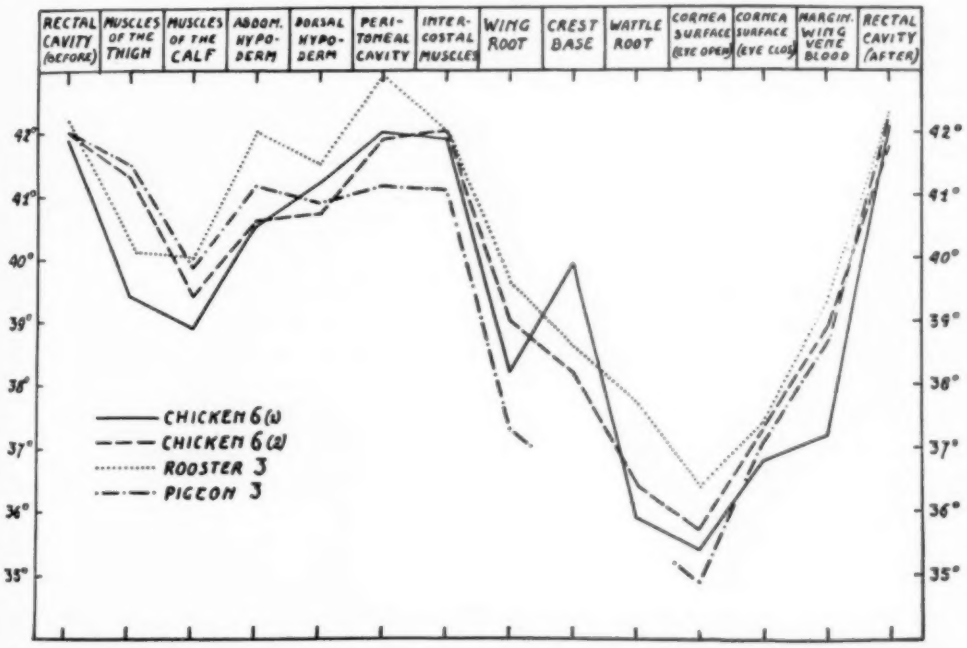

Fig. 1. Examples of superficial and deep tissue temperatures in birds (2 chickens, 1 rooster and 1 pigeon).

We believe that we have disproved these assumptions. We have repeated the experiments of Giovanni Truffi, and have accurately measured, by means of thermocouples, the temperatures of various parts of the animal body during experiments involving ten hens, three roosters and eight pigeons. In the first place, as is shown by the accompanying graph (figure 1), the temperatures of various parts of the bodies of these animals vary

* Presented at the St. Louis meeting of the American College of Physicians, April 21, 1937.

From the Institute of Hygiene and Bacteriology of the State University of Ghent, Belgium.

tremendously, notably from 35° C. to more than 42° C. (95° F. to 107.6° F.). Hence, if treponemas lodge in cool parts, they may retain their virulence. Secondly, we believe that the experiments of Giovanni Truffi must have been carried out under peculiar conditions, because we were not able to confirm his results.

The blood, as well as emulsions of the liver, spleen, brain, spinal cord, and several lymph nodes of our 21 experimentally infected birds, failed to produce a single syphilitic lesion, when injected into the testicles of 42 rabbits which survived for at least four months. The popliteal lymph glands of these rabbits also remained sterile.

Furthermore, we must call attention to the fact that, as a syphilitic strain is passed through a series of rabbits, it gradually becomes more virulent for this animal. It is not far afield to assume that this is connected with an increased resistance of the strain to temperature. Giovanni Truffi worked with a strain which had serially passed through the bodies of hundreds of rabbits, since it was isolated about 30 years ago. As our own strains have aged, they have become more virulent. In some cases also, they seemingly have become more thermo-resistant. In 1928 we were able to prevent the appearance, or to cure syphilomata of rabbits in 7 out of 13 experiments, by transposing the testicles for several hours into the abdominal cavity (table 1). In 1935 (same table), this was possible in only three out of 22 experiments.

We have shown that there is a considerable variation of the temperature of different parts of the body of normal birds. Tables 2 and 3 show that this variation also exists in the organs and tissues of normal rabbits. It should be noted (table 3) that there is a variation of more than two and a half degrees centigrade (5.5 degrees Fahrenheit) in the temperatures of such a small organ as the eye of this animal. Even when hot baths are given to a rabbit (table 4), there is a variation of temperature in the various parts of the body.

Table 5 shows that the position of the active and of the inactive electrode, during local diathermy of the deep organs of the true pelvis, has a decided influence on the temperature obtained in the cervix (6 to 14 measurements were made on each of 12 women, to obtain the averages recorded in the last column.)

Analogous variations with the mode of application were observed, during local diathermy, in different parts of the abdominal cavity of the rabbit. This was accomplished by means of accurately calibrated thermocouples, inserted through the anal opening, as is shown by the roentgen-rays (figures 2 and 3).

When temperatures are measured in the electrical or electromagnetic high frequency fields, the latter must be discarded if resistance pyrometers or thermocouples are used. Mercury thermometers are only reliable, within the fields, when inserted into the tissue. On the contrary, quartz and even

TABLE I

Temporary Ectopisations, into the Abdominal Cavity, of Rabbits' Testicles Inoculated with Syphilis or Carriers of Syphiloma Nodules*

Case	Trepo-nemas before	Duration of displacement (in days and hours)	Extreme rectal temperatures (in degrees centigrade)	Results				Transfer of the lymph glands	Remarks
				Treponemas (by puncture)		Clinical aspect			
				Immediately	Later	Immediately	Later		
			A. EXPERIMENTS MADE IN 1928–29: *immediate displacement after inoculation*						
1	(L) : P	51 d.	38.7–39.6	Absent	Absent	N	Normal		Control (R) : P
			Displacement of syphiloma nodules						
2	P	3 d.	38.8–39.7	P mobile	Immobile 5th day	P	N 13th day	P	
3	P	3 d.	38.5–39.3	P immobile	P mobile	P	Evolution P		
4	P	2 d.	38.5–39.3	P mobile	Immobile 4th day	P	N 21st day		
5	P	2 d.	38.6–39.4	P mobile	P mobile	P	Evolution P		
6	P	24 h.	38.9–39.8	P mobile	Immobile 3d day	P	N 14th day	P	
7	P	24 h.	38.9–39.9	P mobile	Immobile 3d day	P	N 13th day		
8	P	24 h.	38.5–39.3	P mobile	P mobile	P	Evolution P		
9	P	12 h.	38.7–39.4	P mobile	P mobile	P	Evolution P		
10	P	12 h.	38.6–39.6	P mobile	P mobile	P	Evolution P		
11	P	7 h. 30 m.	38.6–39.5	P mobile/agon.	Immobile 24th hour	P	N 11th day		
12	P	6 h.	38.6–39.7	P mobile	P mobile	P	Evolution P		
13	P	3 h.	39.5–40.	P immobile	N 24th hour	P	N 4th day		
			B. EXPERIMENTS MADE IN 1935–36: *immediate displacement after inoculation*						
14		8 d.	38.6–39.5	Absent	Absent	N	Normal	P	Late enteritis
15		7 d.	38.7–39.6	Absent	Absent	N	Normal	P	
16		5 d.	38.6–39.4	Absent	P (autopsy)	N	Normal		Death the 5th day
17 to 35		1 to 8 d.	38.4–39.7	Absent	P	N	Evolution P		

* P = positive, N = negative, L = left, R = right, agon. = agonizing.

TABLE II

Average Temperatures (in Degrees Centigrade) of Various Organs and Tissues, in the Normal Rabbit

Organs and tissues	First series of measurements	Second series of measurements
Axillary glands	39.7	—
Rectum	39.48	39.80
Liver	—	39.69
Lungs	—	39.29
Upper cervical vertebrae	39.16	—
Testicle displaced into abdominal cavity	39.05	39.28
Costo-chondral articulation	39.04	39.46
Muscles of the abdominal wall	—	39.37
Occipital periostéum	39.01	—
Sternum	38.99	—
Skin of the abdominal wall	—	38.73
Parietal periosteum	38.62	38.18
Brain	—	38.45
Mouth cavity	38.28	39.35
Submaxillary glands	38.24	—
Inguinal glands	38.15	38.32
Retina	38.10	—
Popliteal glands	38.08	38.88
Testicle, 1 min. after replacement	37.92	38.05
Dorsal skin	37.91	—
Frontal periosteum	37.90	37.25
Testicle, 2 min. after replacement	37.44	37.89
Skin of the base of the ear	37.42	37.69
Subarachnoidal cavity	—	37.35
Hip muscles	—	37.34
Skin of the lower eye-lid	—	37.07
Caudal vertebrae	37.05	—
Nasal bone	36.98	35.59
External malleolus	36.77	—
Testicle, 5 min. after replacement	36.74	36.97
Tarsus	36.45	—
Skin of the middle of the ear	—	36.00
Genital mucosa	—	35.93
Center of the cornea (eye open)	35.93	35.50
Metatarsus	35.17	—
Phalanges	34.41	—
Subungual skin	—	34.20

TABLE III

Average Temperature of Different Parts of the Eye, in the Normal Rabbit

Place of measurement	Degrees centigrade
Vitreus	38.3
Retina	38.1
Sclera	37.4
Anterior surface of the iris	37.2
Bulbar conjunctiva	36.8
Palpebral conjunctiva and posterior surface of the nictitating membrane	36.7
Posterior surface of the cornea (between center and periphery)	36.6
Upper eye-lid (4 mm. depth)	36.6
Anterior surface of the nictitating membrane	36.5
Upper eye-lid (average)	36.0
Cornea (average)	36.0
Center of the anterior surface of the cornea	35.8
Periphery of the anterior surface of the cornea	35.7
Cornea (between center and anterior surface)	35.5
Upper eye-lid (2 mm. depth)	35.4

TABLE IV

Temperatures (Degrees Centigrade) Simultaneously Measured at 5 Minute Intervals, for Different Parts, in 2 Normal Rabbits Treated by Hot Baths

Bath water	Testicle kept exterior	Rectal cavity	Right popliteal gland	Left popliteal gland	Mouth cavity	Right axillary folds	Left axillary folds
First experiment:							
42.6	40.4	39.4	40.6	40.4	38.1	38.8	38.8
42.5	40.4	39.9	40.4	40.8	38.6	38.6	38.6
42.	40.8	40.7	40.8	41.6	39.1	39.	39.4
41.5	40.8	41.1	40.	41.	39.2	39.2	39.4
42.	40.8	40.8	40.4	40.8	39.7	39.2	39.2
42.	40.4	40.9	40.4	40.4	39.7	39.6	39.6
42.	40.4	41.1	40.4	40.	39.8	39.2	39.6
42.	40.	41.1	40.4	40.4	39.9	39.6	39.8
42.	39.8	41.1	40.	40.	40.	38.8	39.2
42.	40.	41.1	40.	40.	39.9	39.2	39.2
Second experiment:							
42.3	41.4	39.4	40.2	40.6	38.2	39.	39.
42.	41.8	40.	41.6	41.8	38.4	39.8	39.8
41.5	42.2	39.7	41.8	42.2	38.5	40.	40.2
41.5	42.2	40.	42.	42.4	38.8	40.4	40.4
41.8	42.2	40.1	42.4	42.4	38.8	41.	40.6
42.1	42.6	40.1	42.4	42.6	39.	40.6	40.6
42.	42.2	40.2	42.2	42.4	39.	40.2	40.2
42.	42.	40.3	41.6	42.6	39.	40.2	40.6
41.8	41.4	40.3	41.8	41.6	39.1	40.	40.6
41.8	41.	40.3	41.8	41.8	39.2	40.2	40.2

TABLE V

Average of Maximum Temperatures Reached by Cervix Uteri, in Women, during Medium Wave Diathermy of the Deep Organs of the True Pelvis

Location of active electrode	Location of inactive electrode	Relative size of the two electrodes	Different groups of cases	Calculated average temperature (degrees centigrade)
Above symphysis	Buttocks	1/3	27 to 29	221.88/6 = 36.98
id.	id.	1/2	30 to 36	525.68/14 = 37.55
Across the lower abdomen	id.	2/3	42 to 44	228.14/6 = 38.02
Above symphysis	id.	2/3	37 to 41	380.3/10 = 38.03
Across the lower abdomen	id.	1/1	45 and 46	152.9/4 = 38.22
Vagina	Iliac fossae	1/5	1 to 4	317.54/8 = 39.69
id.	Above symphysis	1/7	5 to 8	323.75/8 = 40.47
id.	Buttocks	1/7	16 to 19	325.61/8 = 40.70
id.	id.	1/6	14 and 15	163./4 = 40.75
id.	Across the lower abdomen	1/11	9 to 13	409.1/10 = 40.91
id.	Buttocks	1/12	23 to 26	328.76/8 = 41.09
id.	id.	1/11	20 to 22	246.6/6 = 41.10

glass thermometers filled with benzene or with mineral oil are never affected. (Such thermometers may be of the ordinary, curved or Zondek type.) For instance, when placed in the open air between the electrodes of short or

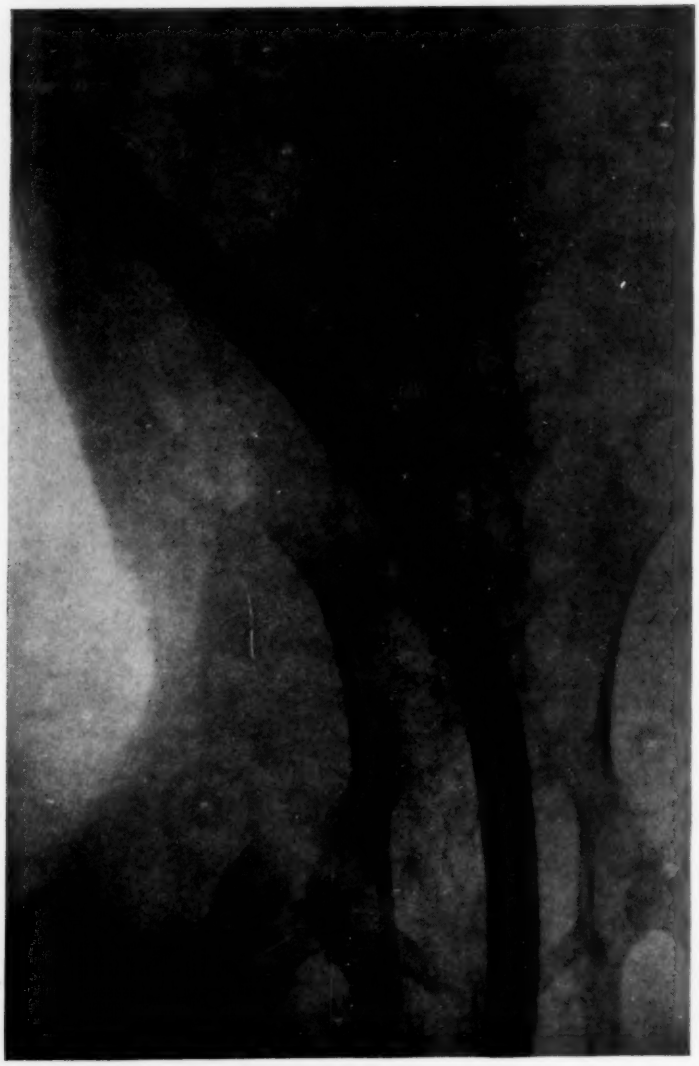

FIG. 2. Roentgen-ray of a rabbit, in which a thermo-electric tube was introduced through the anal opening until a definite resistance was met: the end reaches the left hypochondrium.

ultra-short wave apparatuses, or surrounded by the coil of an "inducto-therm," they do not record a fall of the temperature directly after the current has been turned off. Figures 4, 5 and 6 show syphilitic rabbits being treated by a "diathermax" apparatus (medium waves), an "inductotherm" (short

waves) and an "ultrapandoros" (ultrashort waves), the temperature of a syphiloma or a popliteal lymph gland, of the neighboring air, of the mouth and the rectum being measured, in the course of the experiments, with the

FIG. 3. Same roentgen-ray as in figure 2, the tube having been pushed farther: the end bends towards the left iliac fossa.

benzene or mineral oil thermometers, without it being necessary to turn off the current.

In these cases, there is a great variation of the temperature of the measured infected regions (syphilomas and popliteal lymph glands), as long as they are not covered. On the contrary, if in similar experiments these

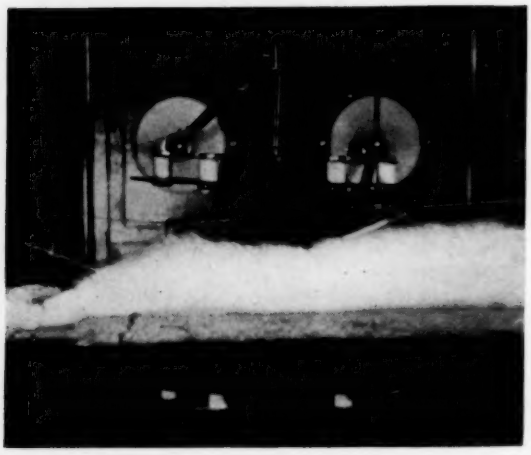

FIG. 4. Comparative thermic measurements of a left testicular syphiloma in the rabbit, of the neighboring air and of the rectum, in the course of a treatment by a "diathermax" apparatus (electric short wave diathermy of 18 meters) applied bipolarly: the special Zondek thermometer was placed within the syphiloma.

FIG. 5. Comparative thermic measurements of a left popliteal lymph gland in the rabbit, of the neighboring air and of the rectum, in the course of a treatment by an "inductotherm" (magnetic short wave diathermy of 25 meters), the cable forming a solenoid around the body; the special Zondek thermometer was placed within the tissue at the level of the gland.

regions are insulated against heat-loss by covering them with cotton, high local temperatures can regularly be obtained.

Some animals die of heat stroke during such experiments. But if the temperature of a testicular syphiloma is raised to 42° C. (107.6° F.) for one hour by this method, a destruction of the syphilitic germ in the organ usually results; this is frequently not the case when a same temperature is produced in a popliteal lymph gland.

Thus, in our experience, the increased thermo-resistance " in vivo " of the treponemas of the superficial lymphatic system of the rabbit also exists against short and ultrashort wave radiation. Besides, neither the wave length nor the physical modality used has any effect *per se* on killing the

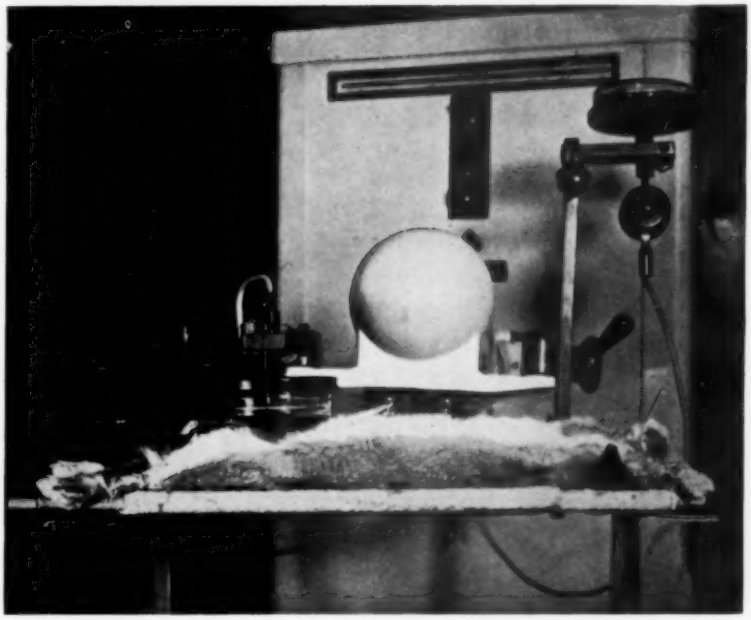

FIG. 6. Comparative thermic measurements of a left testicular syphiloma in the rabbit, of the neighboring air, the rectum and the mouth, in the course of a treatment by an "ultrapandoros" (electric ultrashort wave diathermy of 4 meters), applied monopolarly: the special Zondek thermometer was placed within the syphiloma.

treponemas; the important factor is the height of the temperature of the lesion.

It is well known that if a rabbit with a testicular syphiloma is immersed in a hot bath, the syphiloma disappears under definite conditions of temperature and time. If the entire animal develops a sufficiently high fever as a result of the hot bath and if the infected testicle does not come in contact with the water, its syphiloma heals or not, according to whether it is surgically fixed within the abdominal cavity, or is in a position where it is kept cool. This disproves the rather absurd claim advanced many years ago, that water has anything to do with healing syphilis. It proves that the favorable healing effects are caused by heat.

We have also demonstrated that in man, whatever are the physical heating procedures used, neither the mobility nor the virulence of the treponemas nor the clinical aspect of the syphilitic lesions is affected, if the local temperature is not high enough. The exposure of a lesion to an intense electric field does not produce any changes, even if the intensity is so strong as to burn the superficial tissues.

Finally, we have experimented "in vitro" with an emulsion of an Ehrlich sarcoma of the mouse, with various bacterial cultures, and with an emulsion of guinea pig blood rich in trypanosomas. If any of these products are exposed to the action of short or ultrashort waves, a sterilization can be obtained. If, however, the test tubes containing the products are cooled at the same time by means of air or flowing water, this is not true, if the temperatures of the emulsions and cultures are kept low enough to prevent the thermic action of the electric waves. Therefore, it is apparent that, in these experiments also, we are not dealing with any specific wave effect. As an example, table 6 proves this fact for *Trypanosoma gambiense*, treated by short magnetic waves.

There are some paradoxical facts which we have recently observed when heating testicular syphilomas of rabbits by means of certain medium diathermic currents. It sometimes happens that, even if local temperatures which should be adequate for healing the lesion are applied, no healing effect is obtained. It also happens occasionally in this treatment that if a lesion is cooled by air-blowers to such an extent that no healing should result, the treponemas nevertheless disappear, and the lesion heals after a few days.

TABLE VI

Influence of Short Magnetic Waves of 25 Meters ("Inductotherm") on an Emulsion of Guinea-Pig Blood Very Rich in Trypanosomes (Arsenoresistant Strain of *Trypanosoma gambiense*)

Duration of irradiation (in minutes)	Temperature (in °C.) of emulsions	Density in mobile Trypanosomes	Aspect of parasites
A. Maximum diathermy without cooling:			
60	34.	+++	Very mobile
90	39.	+++	id.
115	43.	++	Less mobile
120	44.5	+	Some moving slowly, some already dead
125	46.	−	All dead
130	47.	−	Lysis *
B. Same diathermy but with cooling:			
0	20.	+++	Very mobile
60	30.	+++	id.
120	32.	+++	id.
160	33.	+++	id.†
C. Emulsion kept, without being irradiated, at room temperature:			
300	20.5	+++	Very mobile

* Inoculation in the guinea-pig negative.
† Inoculation in the guinea-pig positive and persistence of arsenoresistance.

These paradoxical reactions may possibly be explained by a change in thermo-resistance of the germ, by some effect of high frequency currents on the neuro-vegetative system of the rabbit, or by other as yet unknown factors. The reaction of the whole organism becomes evident in these cases. At present such observations are confined to the rabbit.

Following the ideas of Walter M. Simpson and Clarence A. Neymann that a judicious combination of chemotherapy and pyretotherapy might accomplish more than if either therapy is used alone, we devised a method by which rabbits could be treated with artificial fever and appropriate chemical substances. A cabinet was constructed of wood, without the use of nails or metal parts. The animal was heated in this cabinet by hot air alone (figure 7) or by hot air combined with electromagnetic induction (figure 8).

FIG. 7. Special heating cabinet for general aero-pyrexia in the rabbit.

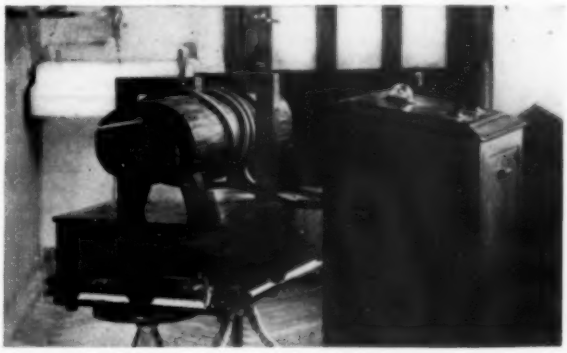

FIG. 8. The same cabinet as in figure 7, with the cable of an "inductotherm" wound around it, for general aero-inductopyrexia in the rabbit.

If air alone was used for heating, we began with a temperature of 55° C. (131° F.), and continued at about this level until the rectal temperature reaches 41.5° C. (106.7° F.); at this point the temperature of the air of the cabinet is reduced to 42° C. (107.6° F.).

By careful technical manipulation of the air temperature and the intensity of the magnetic field, the rabbits' fever may be maintained at approximately 42° C. (107.6° F.) for one-half hour. The rabbit is more sensitive to artificial fever than man, probably because of its deficiency in perspiration. It was, therefore, impossible to maintain the temperature for as long a period as has been possible in man.

Nevertheless, an average temperature of more than 42° C. (107.6° F.) was reached in 11 rabbits which survived. Six of these animals were treated with artificial fever alone, while five were treated with artificial fever combined with arsphenamine. For purposes of comparison, 5 rabbits were treated with the same doses of the drug without fever.

The results appear in table 7. The lymph gland transfer into the testicles of a new series of rabbits was positive in 2 of the 5 animals treated only with arsphenamine. Two of the 6 rabbits treated with fever alone also gave positive transfers. As yet we have not been able to secure positive transfers from any of the 5 rabbits treated with fever and arsphenamine.

TABLE VII

Physicothermo- and Chemotherapy, Single or Combined, of Rabbits Recently Cured of Testicular Syphilomas

Rabbits	Age of syphilis at the beginning of treatment	General hyperthermia				Number of injections of 0.25 c.c. of "solusalvarsan" per Kg.	Lymph gland transfer	
		Number of heatings	Intensity of each heating				Time after the end of treatment	Result
			Duration	Extreme temperatures (in degrees centigrade)	Average temperature (in °C.)			
Solusalvarsan-therapy:								
1	4 months	—	—	—	—	3	1 month	N
2	id.	—	—	—	—	3	90 days	P
3	id.	—	—	—	—	3	2 months	P
4	id.	—	—	—	—	3	2 months	N
5	id.	—	—	—	—	3	3 months	N
Aerothermotherapy:								
6	4 months	3	30 min.	42. /42.7	42.5	—	1 hour	P
7	6 months	3	id.	42.1/42.8	42.4	—	90 days	N
8	id.	3	id.	42.3/42.6	42.5	—	2 months	N
9	id.	3	id.	42.2/42.5	42.3	—	6 months	N
Inductotherm with the air at about 42°:								
10	4 months	3	30 min.	42.1/42.6	42.5	—	1 hour	N
11	id.	3	id.	42.4/42.7	42.6	—	8 days	P
Combined treatment:								
Aerothermotherapy and solusalvarsan-therapy:								
12	4 months	3	25 min.	42.3/43.	42.5	3	1 hour	N
13	8 months	3	30 min.	42.1/42.5	42.2	3	2 months	N
14	id.	3	id.	42. /42.9	42.3	3	6 months	N
Inductotherm (with the air at about 42°) and solusalvarsan-therapy:								
15	4 months	3	25 min.	42.1/42.8	42.4	3	11 days	N
16	5 months	3	30 min.	42. /42.6	42.2	3	2 months	N

(*) P = Positive, N = negative.

We realize that these results are inconclusive. First of all, not enough experimental data are available. Secondly, not enough time has elapsed, either between the end of the treatment and some of the transfers, or since the transfers were made. Thirdly, negative results of lymph gland transfers, even when made in optimum conditions, are not absolutely conclusive. We are now working with a larger series. We believe, however, that the results achieved thus far are suggestive.

We have not employed serological tests for our rabbits because, as has been shown in our previous publications, rabbits, when infected only with the pallidoid treponema (*Spirochaeta cuniculi*), may give positive serological tests. Syphilitic rabbits may give negative tests. Normal rabbits may even give positive tests. Serological tests are, therefore, valueless in this species.

Conclusions

1. The ideas advanced by Giovanni Truffi that the *Treponema pallidum* remains virulent after passage for one hour through the bodies of birds have been disproved.

2. The position of the active and of the inactive electrode during local diathermy of the abdominal organs, in the rabbit and in man, has a decided effect on the deep temperatures reached.

3. Quartz or glass thermometers filled with benzene or mineral oil can be employed for the measurement of temperatures in high frequency fields. Such thermometers are not affected by electromagnetic waves.

4. There is a difference "in vivo" in the thermo-resistance of the *Treponema pallidum* of the external syphilitic lesions of rabbits and man, compared with the treponemas found in the lymph glands of syphilitic rabbits. In the latter case the thermo-resistance is so great that it surpasses that of the organism of the host.

5. Neither the wave length nor the physical modality used has any effect *per se* on killing the *Treponema pallidum* within the tissues. The important factor is the height and duration of the temperature of the lesion. The healing effect must be considered in the light of the temperature variations which exist in various parts of the animal body.

6. Paradoxical and unexplained results after treatment with diathermy occasionally occur in rabbits. This is a sign of the reaction of the animal organism as a whole.

7. If bacterial cultures, treated "in vitro" with intense short or ultra-short wave radiation, are cooled so that no heating effect results, they are not affected. The same fact applies to emulsions of an Ehrlich sarcoma of the mouse, and to trypanosomas.

8. A judicious use of the combination of chemotherapy and pyretotherapy seems to be more effective in the syphilitic rabbit than when either therapy is used alone. Serological tests for syphilis are valueless criteria in judging the presence, the progress or the persistence of the disease in rabbits.

DRUGS IN THE TREATMENT OF HEART DISEASE*

By Robert L. Levy, M.D., F.A.C.P., *New York, N. Y.*

"The following remarks consist partly of matter of fact, and partly of opinion. The former will be permanent; the latter must vary with the detection of error, or the improvement of knowledge. I hazard them with diffidence, and hope they will be examined with candour; not by a contrast with other opinions, but by an attentive comparison with the phoenomena of disease." With this paragraph, William Withering, in his *Account of the Foxglove*, published in 1785, opens the chapter dealing with "Practical Remarks on Dropsy, and Some Other Diseases."[36] Certainly, there could be no more appropriate comment with which to begin this discussion.

In any therapeutic program, the use of drugs is but one form of procedure. In the treatment of cardiac disorders, medicinal remedies play an important part because in many conditions they are strikingly effective; often their proper use is responsible for the saving of life. They serve three main purposes: (1) to cope with acute upsets; (2) to restore the function of a failing heart and to maintain it at the optimum level of competency; (3) to prevent the occurrence of disturbances in the circulation, or their recurrence once they have appeared and been adjusted. Numerous remedies have been proposed and tried. Some have stood the test of clinical usage; others, though of proved value, have been supplanted by better drugs which newer studies have made available; many have been found wanting and have been discarded.

It would be neither feasible nor profitable to attempt, at this time, a consideration of all medicinal substances which are known to have an action on the circulation. A few of the more important have been selected which, in the light of current concepts, are regarded as exerting a beneficial action. In its presentation, the material has been divided according to various clinical conditions which can be aided by drug therapy rather than, primarily, into groups of drugs. Although, in some instances, this method calls for repetition, it seems of more practical value; for even though the same remedy may be discussed more than once, the indications for its employment often vary, as well as the manner in which it is best given.

Myocardial Insufficiency

Digitalis.[24] When symptoms and signs indicate that the heart has failed to function adequately as a pumping mechanism, the administration of digitalis is indicated. This statement holds true, regardless of the

* Read before the Cleveland Academy of Medicine, Cleveland, Ohio, December 17, 1937.

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etiological type of cardiac disease; nor does it matter whether failure is predominantly of the left or the right ventricle. Many of the older clinicians believed that the foxglove was effective only when the auricles were fibrillating; but accumulated experience has proved that an equally beneficial result is obtained in the presence of regular, sinus rhythm.

The mode of action of digitalis on the heart has been the subject of much study. It exerts its influence in part through a direct effect on the cardiac muscle, and in part by stimulation of the vagus nerves. The myocardium reacts by an increase in the amplitude of ventricular contractions. In the normal person, the size of the heart becomes smaller and cardiac output is decreased. In patients with congestive failure digitalis also brings about diminution in cardiac size; but when the heart is dilated, shortening of the muscle fibers is accompanied by increased cardiac output and hence, improvement in the state of both pulmonary and systemic circulations.[29, 31]

The effect on the auriculoventricular conduction system, which, in cases of auricular fibrillation is responsible for slowing of ventricular rate and, in those with normal rhythm, may cause varying degrees of heart block, is due to a double action. There is depression of the junctional tissues and vagal stimulation. Both of these effects can be demonstrated by observing the response to atropine after giving digitalis to patients with auricular fibrillation. There is partial release of the vagus, with increased ventricular rate; but the level of tachycardia is not as high as before digitalis was given, and the effect on the T-wave of the electrocardiogram persists.

When regular rhythm prevails, the heart rate is not slowed by a direct action. One of the compensatory mechanisms for maintaining the circulation when the heart has failed, is acceleration of rate. When ventricular discharge is increased, there is no longer need for this reflex mechanism to operate; with adjustment of the circulation, the heart beats more slowly. Nor is any specific change induced upon either systolic or diastolic blood pressure; such alterations as may occur are due to modifications in general circulatory dynamics. Hypertension, therefore, is not a contraindication to the use of digitalis; frequently, with the relief of heart failure, the level of the pressure becomes lower.

The diuresis which occurs after digitalis administration is not due to stimulation of the renal epithelium. It is the result of improvement in the general circulation. Venous stasis in the kidneys is relieved and an adequate flow of blood through them is resumed. This point must be kept in mind in relation to the use of diuretics.

The choice of a preparation is of some importance. The chemistry of the digitalis bodies is still imperfectly understood. Various glucosides have been isolated and numerous so-called "purified" substances are on sale. There is no better form of digitalis for oral use than the whole leaf, dispensed as tablet, pill or capsule. The tincture, even though active, has an unpleasant taste and necessitates careful measurement of each dose. The discrepancy between the volume of the drop and the minim makes for con-

fusion and uncertainty. The infusion, because of its instability, has been generally discarded. For intramuscular or hypodermic injection, liquid preparations are marketed in ampules, which should be of hard glass to prevent deterioration. Soft glass yields alkali which, in time, renders the contents inert.[21] On those rare occasions when intravenous injection seems imperative, crystalline strophanthin is the drug of choice.

Biological standardization of digitalis products, necessary because an accurate method of chemical assay is not available, has become the usual practice with manufacturers. Although the one-hour frog method is still recommended in the U. S. Pharmacopoeia, some modification of the intravenous cat method, introduced by Hatcher and Brody in 1910, has come into widespread usage and is generaliy favored. Approximately 0.1 gm. (1½ gr.) of powdered leaf, 15 minims (1 c.c.) of tincture and 0.1 mg. (1/60 gr.) of strophanthin are equivalent to 1 cat unit, as commonly prepared. Dosage is expressed in terms of cat units. Assay on animals is far from ideal. The results are not always transferable to man because of variability in absorption and because biological activity and therapeutic potency do not always parallel each other. It is the best method now known and has served to do away with the gross variations in strength which, twenty-five years ago, made even approximate dosage entirely a matter of trial and error.

When possible, it is best to give digitalis by mouth. The oral route is simple, safe and efficacious. If the dose is adequate, a beginning effect on the heart can be obtained in from two to five hours, a maximal effect in from six to twelve hours. In the presence of nausea or vomiting, or after surgical operation, digitalis may be administered by rectum, as the tincture, or in a suppository.[19] Absorption is good and the speed of action is comparable to that observed when similar doses are given by mouth. Intramuscular injections may be made when the oral and rectal routes are not available. Intravenous injection is always attended with some hazard. A high level of concentration is quickly attained and the margin between therapeutic and toxic dose is relatively small. Intravenous injection should never be made if the patient has received digitalis within the preceding week, because of the danger of cumulative effect. Introduction of a digitalis body directly into the circulation is rarely necessary and should be done only in emergencies. As a rule, if the need seems immediate, digitalis will not avail.

The optimal total therapeutic dose varies according to the degree of cardiac insufficiency and the susceptibility of the individual. In general, the more advanced the failure, the greater is the amount required. The total dosage for inducing full effect in a person who has not previously received digitalis within two weeks is between 1.0 and 2.0 gm. (15 and 30 gr.). It is usually safe to administer 1.0 gm. in divided doses during the first 24 hours; these may conveniently be given at intervals of four or six hours. In the second 24 hours, 0.5 gm. may be given in divided amounts at similar intervals. Subsequent therapy depends upon the effects obtained and those

regarded as desirable. If haste is not necessary, smaller amounts may be given over a longer period. Relatively large doses are tolerated by children.

After the restoration of compensation, it is often of advantage to continue each day the administration of small maintenance doses over a period of weeks, months or years. This is almost invariably necessary in patients with permanent auricular fibrillation, in order to keep the ventricular rate at a properly low level. The optimum rate must be determined in each case, but is usually between 70 and 80 per minute, at rest. A daily ration is useful also in older persons with enlarged hearts; in them a continued "tonic" effect may prevent the recurrence of failure, particularly if the amount of cardiac reserve is small. Digitalis disappears from the body, either by elimination or destruction, at the rate of approximately 0.1 to 0.2 gm. (1½ to 3 gr.) in 24 hours. But as little as 0.05 gm. or as much as 0.3 gm. daily may, on occasion, be the dose required for holding a continued effect at the desired level. Each patient, in this respect, is the subject of experiment.

Calculation of dose according to body weight is not necessary. It affords to the physician a false sense of accuracy based on a formula which is subject to a wide margin of error. Skillful use of digitalis requires careful study in every case. Standardization of the drug and the establishment of satisfactory clinical criteria for therapeutic action have, in large measure, eliminated the necessity for inducing toxic effects in order to be certain that enough has been given. The oft quoted dictum of Withering —"let it be given until it either acts on the kidneys, the stomach, the pulse, or the bowels"—no longer holds good with respect to stomach and bowels. Deliberately to poison the patient is not the goal of modern therapy.

Yet, in spite of reasonable care, toxic effects occasionally are induced. They must be watched for and, immediately upon the appearance of one of them, the drug should be discontinued or the dosage curtailed. Nausea, vomiting, headache, diarrhea and the occurrence of premature contractions are among the earlier evidences of intoxication. Mental confusion and visual disturbances are less frequently encountered. In the more advanced stages of poisoning, auricular fibrillation, auriculoventricular heart block and ventricular tachycardia may occur. Ventricular tachycardia is of particular significance; for giving more digitalis, after it has appeared, can convert it into ventricular fibrillation and cause sudden death.

Squill. Prepared from the bulb of the sea onion, squill is one of the oldest medicinal agents. The earliest reference to it is found in a prescription contained in the Ebers papyrus, about 1500 B.C. For a long time it fell into disuse, apparently because of its tendency to cause nausea and vomiting. It enjoyed renewed waves of popularity, first in the middle of the eighteenth century, largely through the writings of van Swieten; and again, in the past 15 years, as a result of the isolation of various so-called "active principles." Most of these, however, have been only a little purer than the crude extracts; and because of their poor absorption from the

gastrointestinal tract they have rightly been regarded as undesirable substitutes for digitalis.

Recently, by modifying the methods of extraction, a new preparation of squill has been made and is now marketed under the trade name, "Urginin." It is a mixture, in approximately equal proportions, of two of the active, water-insoluble glucosides—crystalline scillonin A and amorphous scillonin B. For oral use, it is put up in tablets containing 0.5 mg. each.

A clinical study of urginin was made during the past year in our department at the Presbyterian Hospital, by Chamberlain and Levy.[5] It was found that, in patients with cardiac insufficiency, urginin exerted an action on the heart like that of digitalis. The effects were noted in the presence of regular rhythm as well as when the auricles were fibrillating. The therapeutic potency of urginin, in terms of cat units, was about one-half that of digitalis. Thus, approximately two cat units of urginin were required to induce effects, both therapeutic and toxic, comparable to those induced by one cat unit of digitalis. This difference in activity may be ascribed to less complete absorption or more rapid elimination in the case of urginin.

A satisfactory scheme of dosage, when no digitalis or urginin has been given for at least ten days preceding, was: 1.5 mg. (3 tablets) three times a day after meals for two days; 1.0 mg. (2 tablets) twice daily until the desired effects were produced. The daily maintenance dose ranged from 0.5 to 2.0 mg.; the average was 1.0 mg. (2 tablets).

Toxic effects noted were nausea, vomiting, diarrhea, transient auricular fibrillation, auriculoventricular nodal rhythm and varying degrees of heart block. But every patient without previous nausea was able to retain urginin if given after a meal in amounts not exceeding 1.5 mg. (3 tablets). Premature beats as evidence of intoxication were not observed.

The effects on the electrocardiogram were similar to those seen after digitalis.

It was concluded that urginin is an effective cardiac remedy. It offers no advantages over digitalis with respect to its action in myocardial insufficiency. But it serves a purpose in that occasionally, patients in whom digitalis induces nausea, vomiting or diarrhea, are able to take urginin without suffering from unpleasant symptoms. It may be useful also when a patient harbors an unfounded prejudice against the use of digitalis.

Strophanthin. Because of the variability with which strophanthus is absorbed from the gastrointestinal tract, it is unsuitable for oral administration. Crystalline strophanthin (ouabain), derived from the seeds of *Strophanthus gratus,* is particularly useful for intravenous injection, because its crystalline character and known chemical composition make accurate dosage possible. An initial effect is apparent in from 5 to 20 minutes, the maximum effect in from 15 to 50 minutes.[38] If given in fractional doses, it may be administered safely to patients with auricular fibrillation with rapidly beating ventricles, who have not received digitalis within a week.

In them, ventricular rate can be used as a guide of effect. Greater care is necessary when it is given in the presence of regular sinus rhythm, when clinical improvement is the only criterion of full therapeutic effect. In those occasional instances when rapid action seems necessary, 0.5 mg. may be injected at the first dose, to be followed at intervals of one hour or more by 0.1 or 0.2 mg., up to a total dose of 1.0 mg. Treatment may then be continued by the use of digitalis, given by mouth, by rectum or by intramuscular injection.

Amorphous strophanthin, obtained from *Strophanthus kombé* or *hispidus*, is less uniform in composition and is not superior to the various aqueous preparations of digitalis.

Diuretics. (*a*) *The xanthine group.* Often rest in bed, curtailment of fluid and salt intake and the exhibition of digitalis promote diuresis and relieve edema. If, after these measures have been tried, there is evidence of continued retention of fluid in the tissues, diuretic drugs are indicated.[16] For use by mouth a member of the xanthine group may be given.[25] Theobromine sodium-salicylate (diuretin) is one of the most valuable because of its relatively slight toxicity. It may be taken in powder or tablet form, in doses of 1.0 gm. (15 gr.), three or four times a day for two or three days, and then repeated at intervals of several days. Theophylline (theocin) may be similarly used in doses of 0.2 gm. (3 gr.) three or four times a day, but is more likely to upset the digestion. Theobromine-calcium salicylate (theocalcin) is a third member of the series, to be given in doses of 1.0 gm. (15 gr.) three or four times a day.[30] Theocalcin, being well tolerated, is of particular value when it is desired to maintain mild diuresis over a period of days or weeks.

(*b*) *The mercurials.* Mercupurin and salyrgan have largely supplanted the xanthines.[8, 9, 33] They are more rapid in action and more potent, yet relatively non-toxic. Renal irritation is rarely observed. They are given preferably by intravenous injection, in doses of 1 to 3 c.c., the smaller amount being injected first to test the patient for possible idiosyncrasy to mercury. The injection may be repeated at intervals of four to six days when required. Mercupurin, which is a combination of theophylline with mercury, is less irritating to the tissues than salyrgan and can be given intramuscularly, if necessary. Both preparations are available in the form of suppositories; * they are somewhat less effective when given by rectum. The action of the mercurials may be enhanced by administering ammonium chloride or ammonium nitrate for from 24 to 48 hours prior to using the diuretic. These "acid producing" salts are best tolerated in the form of enteric coated pills of 0.5 gm. (7½ gr.) each. As much as 8 to 10 gm. of one or the other must be given in 24 hours, in divided doses, to be effective.[17] Usually mercury alone is adequate; the tendency for the am-

* In the case of mercupurin, the suppositories do not contain theophylline and are known as "mercurin."

monium compounds to cause nausea and vomiting when taken in such large amounts, limits their clinical usefulness.

The xanthines, according to the best evidence, increase glomerular filtration; the mercurials diminish tubular reabsorption. Since these two groups of substances thus differ in their mode of action, they may sometimes be used alternately to advantage.

Sedatives. The late Sir James Mackenzie has wisely said that "little benefit is likely to arise from treatment so long as a patient is worried or sleepless." The cardiac patient who has tossed about, harassed by dyspnea, awakens from a sound sleep refreshed and encouraged, after a hypodermic injection of 15 mg. (¼ gr.) of morphine sulphate or 20 mg. (⅓ gr.) of pantopon. This may be repeated for several nights, or even during the day, until other measures have so improved the circulation that milder sedatives will serve, or none are required. One of the barbituric acid derivatives, such as phenobarbital, or a bromide mixture, given three or four times daily, will often allay restlessness. For insomnia, a barbiturate, such as sodium amytal or nembutal, will assure comfortable nights. A tranquil frame of mind is essential for proper relaxation and coöperation.

Cathartics. Vigorous purging, with evacuation of copious watery stools, is no longer regarded as good practise. Fluid can be eliminated more readily and with less discomfort through the kidneys. The frequent use of bedpan or commode is tiring and requires effort at a time when rest is of first importance. Mild daily catharsis to prevent clogging of the intestinal tract is desirable. At the start, a dose of magnesium sulphate or compound jalap powder rids the bowel of accumulated waste; later, milder cathartics, such as cascara, are effectual, aided, if necessary, by a small, bland enema.

Glucose. The intravenous injection of hypertonic glucose solution has been recommended, particularly by European authors. Sometimes it appears to help in initiating improvement when other measures have failed. The sugar is a nutrient for the myocardium, exerts a diuretic action and sometimes aids in relieving frequent paroxysms of dyspnea. From 50 to 100 c.c. of a 50 per cent solution are injected once or twice daily for several days.

Oxygen. By definition, a drug is any substance used medicinally. Though administered by inhalation, a gas falls into this category. Myocardial insufficiency is often accompanied by a state of marked anoxemia; this can be relieved by increasing the oxygen content of the inspired air to 50 per cent or more.[1] There result elevation of the oxygen saturation of the blood to normal, decrease in pulmonary ventilation and increase in the carbon dioxide concentration of the expired air. The heart rate becomes slower, dyspnea is relieved, cyanosis disappears, as does Cheyne-Stokes respiration, if present. The patient is less restless and within 24 hours may be able to sleep without the aid of narcotics. Part of the burden of a failing heart is lightened. In cases of chronic failure, not yielding to other forms of

therapy, residence in an oxygen tent or chamber over a period of days, or even weeks, has occasionally served to promote diuresis and by so doing, has started a chain of events leading to the recovery of compensation.

Patients with active rheumatic carditis, in our experience, have not responded favorably. Those in whom failure was due to coronary heart disease or hypertension have done well. Prolonged residence in an oxygen chamber has also been found useful in preparing persons with cardiac insufficiency for operative procedures. Cases of hyperthyroidism have been conspicuous in this group. The technic of oxygen therapy need not be given in detail here. The tent is now a familiar apparatus and is quite generally available. For prolonged periods, the chamber is more comfortable, though expensive to install and operate. The nasal catheter may be employed as a measure of moderate effectiveness. The mask recently described by Barach is still undergoing trial.

Cardiac Pain

Paroxysmal pain in the chest may be due to a variety of causes. Upon precise definition of etiology will depend the form of therapy. These remarks will be confined to a consideration of the discomfort commonly referred to as anginal, and due, in most instances, to atherosclerosis of the coronary arteries.

The Nitrites. An attack will usually subside within a few minutes on the cessation of activity or the passing of an emotional upset. Judicious use of one of the nitrites affords prompt symptomatic relief, due to reduction in systemic arterial pressure as well as to dilatation of the coronary arteries. Nitroglycerine is convenient because it can be carried as a tablet, which should be thoroughly chewed before swallowing. A small dose, 0.3 to 0.4 mg. ($\frac{1}{200}$ to $\frac{1}{150}$ gr.) often suffices and may not cause the flushing and headache sometimes so annoying after the larger and more commonly used tablet of 0.6 mg. ($\frac{1}{100}$ gr.). There are cases in which only the larger dose is effective. It is important to insist that nitroglycerine tablets be fresh; after they have been exposed to the air for six to eight weeks, their strength deteriorates. The odor of amyl nitrite, in the form of pearls, has made it less popular than the nitroglycerine tablet. When an attack persists for more than an hour and is not relieved by nitrite, particularly if this is contrary to previous experience, occlusion of a coronary branch should be suspected.

The value of nitroglycerine as a prophylactic, suggested by the Englishman, Leech, in 1893, is not sufficiently appreciated. It was first called to my attention by Professor K. F. Wenckebach, of Vienna, a number of years ago. If a tablet or, if necessary two, be taken prior to anticipated effort or nervous strain, the activity can often be carried through to a painless conclusion. There is no harm in repeating the dose several times during the day. I have seen patients who have taken from 15 to 20 tablets of nitroglycerine daily over a period of years, without apparent harm and with no

loss in effectiveness. In my hands, the routine use of the nitrites, given at regular intervals during the day, has not proved as successful as when necessity or prevention served as indications.

The continued administration of those nitrites having a more prolonged action sometimes leads to marked lowering of blood pressure and syncope. If nocturnal attacks are troublesome, erythrol-tetranitrate, 30 mg. (½ gr.) may be taken immediately before retiring; the effect lasts for four or five hours and sometimes makes undisturbed sleep possible.

Sedatives. The patient subject to anginal attacks is apprehensive. Mild sedatives produce a more equable state of mind and lower the threshold for pain. Phenobarbital, 15 to 30 mg. (¼ to ½ gr.) or a mixture containing 0.6 to 1.0 gm. (10 to 15 gr.) of bromide serves well in this capacity, and may be continued intermittently or continuously for weeks or months.

The Xanthines as Coronary Dilators. Derivatives of theophylline and theobromine enjoy wide popularity for prolonged, daily administration. They are prescribed in the belief that they cause dilatation of the coronary arteries, prevent spasmodic contractions of these vessels and augment the flow of blood through the myocardium. There is at present disagreement as to their value, based both on laboratory and clinical studies. Smith and his collaborators, working with theophylline-ethylenediamine (aminophyllin) have found that in normal dogs, after ligation of a coronary artery the size of the infarct produced was smaller when the drug was given than in controls.[12] Gold and his co-workers[15] were unable to confirm these results in cats. Wiggers and Green,[34] using a different technic, concluded that "an increase in collateral circulation sufficient to be of functional use cannot be attained by use of vasodilating drugs after complete coronary occlusion." Whether these observations are applicable to the diseased human heart has not been demonstrated.

After administering members of this group of drugs to patients, and using adequate controls, different clinicians have reached opposite conclusions. Some, including Evans and Hoyle,[10] and Gold, Kwit and Otto,[14] have stated that the xanthines exert no specific action which is useful in the routine treatment of cardiac pain. Others have been impressed by the favorable results. In a recent study, Brown and Riseman[3] have determined the comparative value of eleven preparations, as judged by the usual clinical criteria, and also by measuring the amount of work, under standardized conditions, which could be done before the appearance of cardiac pain. They found that not all patients respond favorably to purines; but they offer no method of distinguishing between those who do and those who do not. Each preparation was given four times daily—on arising, after lunch and supper, and at bedtime. The order of effectiveness and the individual doses were: theophylline with sodium acetate, 0.25 gm. (4 gr.); theobromine with sodium acetate, 0.5 gm. (7½ gr.); theophylline with calcium salicylate, 0.5 gm. (7½ gr.); theophylline with ethylenediamine 0.2 gm. (3 gr.).

The number and intensity of attacks of anginal pain are subject to wide variations, over a period of months or years, in the same person. Rest, adaptation to limitations, and acquisition of emotional stability often result in great symptomatic improvement in a relatively short time. Appraisal of the therapeutic result based upon the patient's own account is subject to error; the standardized exercise tolerance test, though partially objective, likewise depends for its end-point upon the sensations of the individual tested. In the light of such conflicting evidence, final judgment as to the virtues of the xanthines must be deferred. It is indeed questionable whether they accomplish any good.

Organ and Tissue Extracts. A number of these have been tried, both by mouth and by hypodermic injection. I have never observed any benefit from their use.

Acute Coronary Occlusion

Abrupt closure of a coronary branch, in its early stages, is a medical emergency. Complete rest and relief of pain by generous doses of morphine are the immediate requirements. It is now generally accepted that digitalis, in the absence of signs of cardiac insufficiency, should not be given. If congestive failure develops, or the attack is accompanied by the onset of auricular fibrillation or flutter, with rapid ventricular rate, it must be used in effective amounts, but cautiously. Digitalis is a cardiac stimulant, causing increased force of muscular contraction; the heart which is the site of recent infarction needs rest. The danger of causing rupture of the ventricle by the use of digitalis has been over-emphasized; but the possibility of inducing ventricular fibrillation is real, particularly after the acute phase has passed and the stage of repair is in progress.[2, 13]

If pain is severe or the signs of anoxemia are manifest, administration of oxygen, in concentration of 50 per cent, preferably in a tent, is indicated. Discomfort is lessened and the failing heart is often tided over a critical period. As pointed out by Levy and Barach [22] in 1930, "in certain instances, effective use of oxygen may be responsible for the saving of life."

For collapse, caffeine sodium-benzoate, in doses of 0.3 to 0.5 gm. (5 to 7½ gr.), may be injected into a vein. Should nourishment be poorly taken or vomiting persist, hypertonic glucose solution, 50 per cent, is sometimes helpful. From 50 to 100 c.c. are given intravenously once or twice daily for several days.

The treatment of various cardiac irregularities which may occur as complications is considered in the following section.

Cardiac Arrhythmias

Auricular Fibrillation. In this form of irregularity, in which a circus movement travels an irregular course about the mouths of the great veins, the ventricles usually beat rapidly. Fibrillation of the auricles may be

paroxysmal or permanent. As a rule, it occurs in a diseased heart, most frequently in association with mitral stenosis; under these conditions, it is an expression of myocardial insufficiency and auricular dilatation. Occasionally it is observed in the absence of organic cardiac disease, due to toxic influences or neurogenic disturbances. No matter what the etiology, the first aim of treatment is to slow the ventricular rate. For this purpose, digitalis in full doses is dramatically effective, particularly in rheumatic and coronary heart disease. In cases with toxemia due to bacterial poisons, and in hyperthyroidism, slowing of rate is relatively slight.

When fibrillation is of recent onset, administration of digitalis may be followed by resumption of regular sinus rhythm, due to betterment in cardiac function. Should fibrillation persist, the rate should be brought to a level ranging between 70 and 80, at rest, and held there by proper adjustment of a daily maintenance ration. Patients with permanent auricular fibrillation, in whom the heart rate, undigitalized, is above 80, must take digitalis for the balance of their lives.

In certain cases, normal rhythm can be restored by the use of quinidine.[4] Accumulated experience has shown that the number suitable for the use of this drug is limited. There are dangers from its administration.[20] Such discomforts as tinnitus, nausea, vomiting or diarrhea, though unpleasant, are of minor import. But induction of heart failure, syncope, collapse, embolic phenomena and sudden death are untoward effects which must be considered whenever quinidine is given. The careful selection of suitable subjects minimizes the hazards. Unfavorable criteria are: idiosyncrasy to cinchona derivatives; fibrillation of long standing; cardiac enlargement; mitral stenosis; active carditis; cardiac insufficiency; previous occurrence of emboli to lungs or systemic arteries; complete heart block; bundle branch block; hyperthyroidism. It is at once apparent that only a small group is left. Indications favoring its use are: fibrillation of recent onset; absence of cardiac enlargement; no valvular disease; fibrillation persisting after subtotal thyroidectomy for hyperthyroidism.

Most patients with organic heart disease and auricular fibrillation of long standing (longer than six months) are not greatly improved by restoration of normal rhythm. There is always the possibility, and indeed, the likelihood, that the irregularity will recur, with the sudden onset of a rapid ventricular rate. This requires another period of rest and quinidine therapy. With continuous digitalis dosage, the heart is stabilized and the rate is controlled. The possibility of the occurrence of upsetting episodes at inopportune moments is eliminated. Occasionally, however, when all the usual measures have proved unavailing in combating failure, restoration of normal rhythm may serve to turn the tide; in these rare instances, quinidine may be given a trial.

Before giving quinidine, congestive failure, if present, should be controlled by digitalis, and the ventricular rate should be retarded. The treatment should be carried out with the patient in bed, under careful observation,

preferably with electrocardiographic control. This form of therapy is not recommended for ambulatory cases.

A satisfactory scheme of treatment is as follows, the individual doses being given, by mouth, at intervals of two hours: *First day*, two doses of 0.2 gm. (3 gr.) each; these are to test for a possible idiosyncrasy to cinchona. Normal rhythm may occasionally ensue from this small, preliminary dosage. *Second day*, three doses of 0.4 gm. (6 gr.). *Third day*, four doses of 0.4 gm. *Fourth and succeeding days*, five doses of 0.4 gm. Larger amounts have been used but are not without added risk. The treatment may be continued for a week; though usually, a successful result, if obtainable, is accomplished in from four to six days. If it is necessary to prolong treatment beyond this period, normal rhythm, even though restored, is often not maintained. In a few cases, six to eight doses in a day have succeeded when five have failed. Intravenous injection of quinidine is inadvisable; several fatalities have followed this procedure.

After restoration of normal rhythm, it is desirable to continue with small doses of 0.2 gm. (3 gr.) three times daily, for several weeks. These tend to prevent relapse. Such amounts, or even larger doses, if necessary (0.4 gm. three or four times daily), may be taken for weeks or months without harm or discomfort. A similar plan may be followed, often with conspicuous success, in cases of paroxysmal auricular fibrillation to prevent the onset of attacks. If these recur at frequent intervals, it is best to encourage permanent fibrillation and to control ventricular rate with digitalis.

Auricular Flutter. This is treated with digitalis in the same manner as described for fibrillation. Usually, full dosage is followed by the onset of fibrillation, with subsequent transition to normal rhythm. If flutter persists, quinidine may be tried; but the results, as a rule, are better with the foxglove. Should flutter be converted to fibrillation and normal rhythm not be resumed, quinidine may be used with good effect. There are occasional instances of flutter which are resistant to drug therapy. If the ventricular rate is controlled by digitalis, the patients are able to carry on their usual activities, provided the myocardium is functionally adequate. In several such cases, normal rhythm has been resumed spontaneously, for no apparent reason, after the lapse of months or years.

Paroxysmal Tachycardia. If the attacks are short and infrequent, no treatment is necessary. For the longer paroxysms, recurring at short intervals, simple measures should be tried, such as carotid or ocular pressure, change in posture, the induction of vomiting or forced respiration. Should these prove unsuccessful in terminating the bout, acetyl-B-methylcholine (mecholyl) may be injected hypodermically, in a dose of 20 to 40 mg. It is a powerful stimulant of the parasympathetic nerves. Starr,[28] who has written extensively concerning its use, has had excellent results, and these we have been able to confirm. The attack usually ceases in from one to twelve minutes. Unpleasant symptoms are common; these are dyspnea, substernal pain, vomiting, sweating, flushing and salivation. Atropine, 1.2

mg. given intravenously, will counteract the action of acetyl-B-methylcholine almost immediately, and may be given if the reaction is severe. Attacks of auricular or supraventricular origin are usually stopped by the drug alone. If this is insufficient, carotid pressure during the drug's action is sometimes successful. It is not a dangerous remedy; but it should be used with caution in patients with asthma and in those suffering from conditions responding to epinephrine, which is a physiological antagonist of the cholines.

Quinidine, given by mouth, is occasionally effectual in bringing about reversion to normal rhythm, particularly when the arrhythmia is of the ventricular type.[18] In rare cases an attack is terminated by the intravenous injection of strophanthin. Digitalis or strophanthin must not be given if the tachycardia is of ventricular origin, because of the danger of inducing ventricular fibrillation.

Syrup of ipecac, 8 to 16 c.c. (2 to 4 teaspoonfuls), may be taken orally to induce nausea or vomiting. This is an unpleasant measure; but, by reflex vagal stimulation, it sometimes terminates an attack.

The prevention of paroxysms by drugs is uncertain. Quinidine, in small doses (0.2 gm. three or four times a day) is the most valuable remedy and may be continued, if effective, for an indefinite time. Digitalization, with subsequent daily maintenance rationing, may likewise be tried. Sedatives, in cases in which nervous influences play a part in precipitating attacks, lessen discomfort and lower the threshold for disturbing factors.

Complete Heart Block. Permanent heart block, unless accompanied by heart failure, rarely requires treatment. In certain instances, ventricular standstill or paroxysms of ventricular fibrillation cause dizziness, syncope or convulsive seizures (Stokes-Adams syndrome). It is necessary to know which mechanism is responsible for these attacks in order to carry out appropriate therapy. When ventricular asystole occurs frequently and is of sufficiently long duration to produce the symptoms of cerebral anemia, epinephrine is the best preventive.[11] It is given in doses of 0.5 to 1 c.c. (8 to 15 minims) of the 1 : 1000 solution, by subcutaneous or intramuscular injection. The dose may be repeated as often as every two hours, if necessary. On rare occasions, if ventricular standstill is prolonged, intracardiac injection of epinephrine may save life. When the attacks are due to ventricular fibrillation, epinephrine is contraindicated, for it may perpetuate the mechanism and cause death.

If ventricular standstill tends to recur, ephedrine sulphate is sometimes partially or wholly effective as a prophylactic.[37] Its action is similar to that of epinephrine, but is of longer duration. Ephedrine is given by mouth, in doses of 30 mg. (½ gr.) three or four times a day. Barium chloride, because it increases the irritability of the ventricles, and so lessens the likelihood of standstill, has been employed successfully in a few cases[6]; in patients under my observation, it has been less effective than ephedrine.

It may be given by mouth in doses of 30 mg. (½ gr.) three or four times a day.

In the presence of heart block, quinidine should not be given, since there is some evidence that disturbances in the conduction system favor the development of ventricular fibrillation.

Miscellaneous Conditions

In *diabetes mellitus*, coronary sclerosis is frequently present. Insulin, both by causing hypoglycemia and by sympathetic stimulation, places an added burden of work upon the heart and sometimes induces paroxysms of anginal pain. In elderly diabetics, therefore, insulin should be given with caution; it may cause acute coronary insufficiency and sudden death. It is wiser, in many of these patients, to attempt to control hyperglycemia by dietary measures, even though the urine shows a faint reducing reaction and the level of the blood sugar is somewhat elevated.[32]

The facts concerning the value of intensive anti-luetic therapy in *aortic syphilis* are not yet fully known.[26, 27] It is well to keep in mind two points: first, the cardiologist must have cognizance of the specific nature of the lesions in the heart; second, the syphilologist must appreciate the limitations placed upon anti-luetic treatment by the cardiac disability. As Wile[35] has phrased it in his "therapeutic paradox": "the patient gets well or better of his syphilis, but may die as the result of the dispersion of his syphilitic cardiac lesion." Particularly when involvement of the orifices of the coronary arteries is suspected, the arsenical preparations must be given with great caution; in the judgment of many, it is best, under these circumstances, not to use them at all.[21] Bismuth, mercury and iodide usually can be given with safety.

The use of digitalis in *lobar pneumonia* has occasioned wide differences of opinion. Some have stated that to employ it is dangerous and actually does harm. Others have maintained that every patient with pneumonia should receive it. As a matter of fact, circulatory weakness in pneumonia is not primarily of cardiac origin; the routine use of digitalis, therefore, is not sound practise. The situation was summed up by Cohn in 1935, after a critical analytical study.[7] He concluded that giving digitalis does not seem to influence the course of events in uncomplicated lobar pneumonia. But when congestive failure appears, as it may in patients with cardiac disease, or when auricular fibrillation or flutter occurs, the action of digitalis appears to be beneficial. Under these circumstances, it is sometimes life-saving. The outcome in lobar pneumonia, however, depends primarily upon the severity of the disease itself; and this is determined by the presence of bacteriemia, the number of lobes involved, and the existence of complications.

Conclusion

It is apparent, even from this incomplete discussion, that there are indeed many remedies which can be applied, under different circumstances, in disorders of the heart. Precisely when to prescribe each drug, how much to give, and when to stop, are matters of vital importance. Judgment, based on close observation and experience, is sometimes difficult. Because of the large number of variable factors which modify the picture of disease in human beings, it is not possible to carry out treatment according to a fixed formula. An attempt has been made to describe some of the medicinal tools which have been found useful, and to indicate certain ways in which they may be employed with benefit. Upon the skill of the medical workman will depend, in large measure, the successful outcome of his therapeutic efforts.

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THE USE OF THE MERCURIAL SUPPOSITORY AS A DIURETIC *

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INTRODUCTION

ORGANIC mercurial compounds have been recognized as having valuable diuretic properties since 1920 [1] and have been used with increasing frequency since the introduction of salyrgan in 1924.[2] Later mercupurin (novurit), neptal and mercurosal were used. These drugs proved to be of great benefit in the treatment of cardiac edema, of moderate assistance in the management of nephrotic edema, and of lesser therapeutic value in the edema and ascites of hepatic cirrhosis. In addition to the known limitations, the drugs were objectionable because they were mercurials and thus renal irritants. Great care was therefore necessary in controlling their administration to avoid kidney damage. They were effective only when given intravenously or intramuscularly which entailed some discomfort, and occasionally slough or venous thrombosis as a complication.

In an effort to avoid these latter difficulties, salyrgan has been administered orally, but with poor results.[3] In 1931, Engel and Epstein used salyrgan rectally in 100 c.c. of water with fair results.[4] More recently, rectal suppositories containing 0.5 gm. of novurit † were made available abroad. The active principle was a sodium salt of an organic mercurial combined with theophylline.[5] In this country similar (mercurin) suppositories have been offered containing 0.5 gm. of the organic salt found in mercupurin, without theophylline. Even more recently salyrgan suppositories containing theophylline have become available. Clinical investigators were immediately interested in the efficiency of these preparations.

Parkinson and Thomson [5] made a study of novurit suppository, novurit and salyrgan (each with and without ammonium chloride). They concluded that " novurit suppository is an effective and safe diuretic " and that all three agents are more effective after the administration of ammonium chloride. In the 10 cases reported they avoided the use of digitalis during their determinations. Fulton [6] made a similar study using mercurin suppository, mercupurin and salyrgan on 25 cases and reported favorable results with mercurin suppositories. Herrmann and Decherd [7] published some studies on diuretics including the satisfactory use of mercurin suppositories.

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† Campbell Products, Inc., manufacturers of mercupurin and mercurin suppositories in this country, assure us that their products are identical with novurit and novurit suppositories. According to their statement, the term " novurit suppository " is misleading because the suppositories contain no theophylline.

Method and Selection of Cases

On the wards at New York Post-Graduate Hospital mercurin suppositories have been used on one or more occasions in 12 cases of edema. Of these 12 cases, the edema was due to congestive heart failure in 10, while cirrhosis of the liver was considered to be the causative factor in the other two. In the 10 cases of cardiac decompensation the mercurin suppositories were used in conjunction with the routine treatment of bed rest, sedation, digitalis and ammonium chloride. In three of the cases intravenous mercurials were employed also, and a comparison of the effectiveness of the parenteral and rectal route is available.

In the two cases of cirrhosis of the liver mercurial diuretics were administered by both the above routes; in one case, both before and after ammonium chloride ingestion.

These cases are briefly reported below. The therapy used is indicated by the routine just mentioned and is apparent in the table and figures. The only details included below are those directly relating to the problem, namely, whether mercurial suppositories are an aid in the treatment of edema.

Experimental Observations and Discussion

Case 1. (Table 1) A. B., female, aged 44, was admitted complaining of swelling of abdomen and legs, and "weakness around her heart" for the preceding two weeks. She had been short of breath for two months. Her illness began two years previously with fever, swelling of the joints and "heart trouble." Physical examination revealed a slight degree of dyspnea and orthopnea. Moist râles were present in the bases of both lungs. Her heart was moderately enlarged to the left. A shock and systolic thrill were felt at the apex. A systolic murmur was heard at the apex; the pulmonary second sound was slightly accentuated. The heart rate varied from 96 to 108 per minute and was totally irregular. Blood pressure was 136 systolic and 82 diastolic. The abdomen was moderately distended, with signs of free fluid. The lower extremities showed edema grade one plus.

Case 2. (Table 1) H. I., male, aged 47, was admitted because of shortness of breath and swelling of the abdomen. As a young man (25 years before) he had had rheumatic joint and heart disease and had been given salicylates. He had been entirely well until the week before examination when he noted the above symptoms which became progressively worse. He was unable to sleep at night because of shortness of breath and coughing spells. Although no chest pain was present the patient complained of a pounding heart. Physical examination revealed the patient to be dyspneic and orthopneic. The teeth were carious and infected. The chest was dull over both bases, râles were present, and breath sounds slightly decreased. The heart was somewhat enlarged. There was a systolic murmur at the apex and the pulmonic second sound was accentuated. The apex rate was 126; radial rate 80 with total irregularity; blood pressure 160 systolic and 100 diastolic. The abdomen was obese. The liver was palpated down to the umbilicus and found to be firm and tender. The spleen was not palpated and no ascites was apparent. Ankle edema was absent.

A mercurin suppository was given on the second day but no diuresis was apparent until three days later after ammonium chloride gr. 120 had been given daily.

TABLE I

The Effect of Mercurin Suppositories on the Volume Output of Urine in Cases of Cardiac Decompensation and Cirrhosis of the Liver

	Day of Observation	Water Balance		Ammonium Chloride	Digitalis	Mercurin Suppository	Remarks
		24 hr. Intake c.c.	24 hr. Output c.c.	Gr. Daily	Grains	Time	
Case 1. 44, F. Rheumatic heart disease, inactive.	3	500	600	45	1½		
	4	1280	3350	60	1½	10:00 a.m.	
	5	900	1750	45	1½		
	6	800	1800	60	1½	10:00 p.m.	
	7	1000	2150	60	1½		
Case 2. 47, M. Rheumatic heart disease, inactive.					6		
	2	1600	1100	120		1:15 p.m.	
	3	1550	950	120	1½		
	4	1600	2150	120	1½		
	5	1610	1525	120	1½		
	6	1430	1680		1½		
Case 4. 51, F. Hypertensive cardiovascular disease; obesity; coronary occlusion.	26	1050	525		1½		
	27	1200	2575	90	3	10:00 a.m.	
	28	1550	750	135	1½		
	29	1450	1200	135	3		
	34	1150	790	135	1½		
	35	950	970	135	3		CO_2 49.4 Volumes per cent
	36	650	500	135	1½		
	41	1080	920	135	1½		
	42	1500	2150	135	3	9:00 a.m.	CO_2 52.2 Volumes per cent
	43	1140	735	135	1½		
Case 10. 44, M. Rheumatic heart disease, active; chronic glomerular nephritis; embolism of cerebral vessel.	2	1420	1050		3		
	3	1330	1020		3	11:30 a.m.	
	4	1205	1070		3		
	5	1480	1275	120	3		
	6	1350	1400	120	3		
	7	1480	870	120	3		
	8	1230	950	120			
	9	1650	1300	120		9:00 a.m.	
	10	1690	1350	120			
	11	930	440				
Case 11. 33, M. Syphilis; jaundice; ascites.	30	1150	1050				
	31	2650	1295				
	32	1300	1750			7:00 a.m.	
	33	1375	1230				
	34	1200	2050	90			
	35	3700	2370	90			
	36	1255	1100	90			
	37	1050	2350	90		1:00 p.m.	Expelled after 20 min.
	38	1340	2200	90		10:30 a.m.	Expelled after 20 min.
	39	1300	3050	90			Mercupurin 2 c.c. intravenously
Case 12. 58, M. Arteriosclerotic heart disease; portal cirrhosis.	4	1750	850		3	8:30 a.m.	
	8	1380	820		3	8:30 a.m.	
	12	1290	975		3	8:30 a.m.	
						5:00 p.m.	
	21	1550	600				Mercupurin 2 c.c. intravenously 8:30 a.m.
	32	1620	2050				Mercupurin 2 c.c. intravenously 8:30 a.m.

Case 3. (Figure 1) M. M., female, aged 44, was admitted complaining of shortness of breath, swelling of feet and ankles and of some pain in the abdomen. Three years before the patient first began having asthmatic attacks at night. The attacks were severe and the patient was obliged to sit up to get her breath. Her feet and ankles had been swollen at times for ten months. This was her second admission within six months. She had been receiving digitalis in the clinic. She had precipitated her present cardiac decompensation by over-exertion.

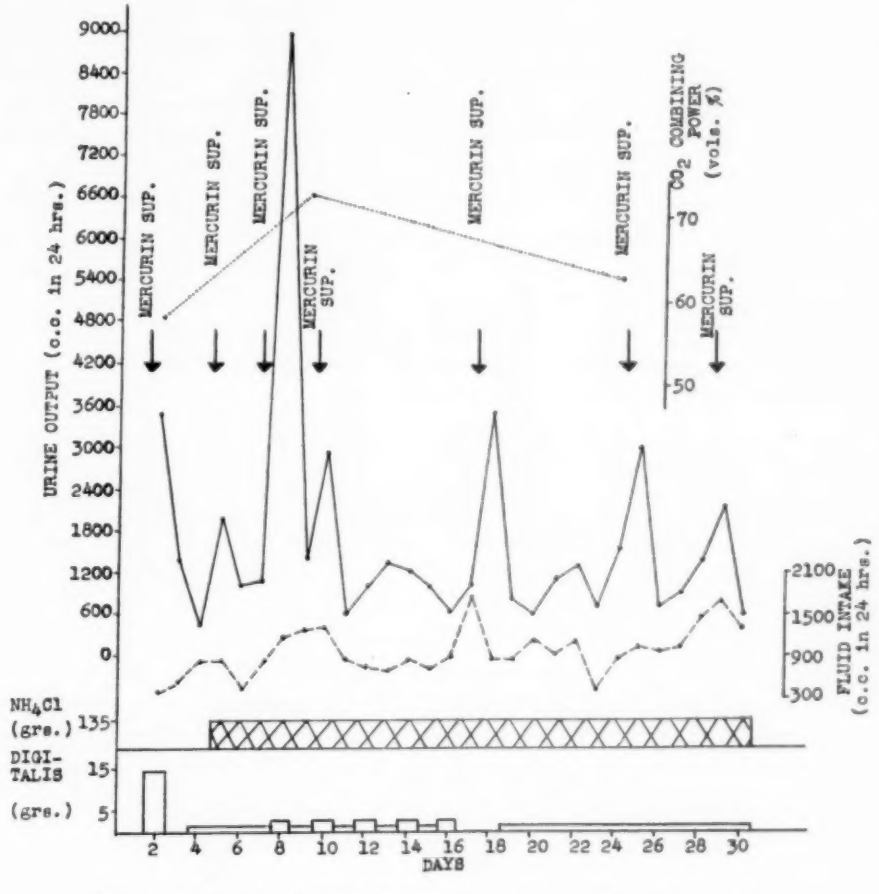

FIG. 1. *Case 3.* Aged 44, F. Hypertensive cardiovascular disease.

Physical examination revealed marked dyspnea, edema and ascites. Her chest was dull on the right to the spine of the scapula. Râles were heard over both bases with decreased fremitus in the right base. The heart was enlarged to the left; a systolic blow was heard at the apex; auricular fibrillation was present with a rate of 92; the blood pressure was 190 systolic and 110 diastolic. The abdomen was greatly distended with fluid. The liver edge was tender and extended 8 cm. below the costal margin. The spleen was not palpated. The legs were edematous to a maximum degree. A pustular eruption on an erythematous base was observed on both thighs.

A graphic presentation of this case (figure 1) shows that on her second day in bed, in response to increased digitalis, bed rest and a mercurin suppository, she had an output of 3,475 c.c. of urine. She had marked anasarca, cyanosis and dyspnea. On the fifth day her condition seemed more critical than on admission. Ammonium chloride gr. 135 daily was begun and another suppository used, with a resultant urinary output of only 1,950 c.c. However, on the fourth day of ammonium chloride, another mercurin suppository was followed by a diuresis of 8,750 c.c. The ammonium chloride was continued and a mercurin suppository used on four subsequent occasions during the next three weeks and in each instance the output exceeded that of the fifth day. This patient on admission and for the first eight days in the hospital was so decompensated that one would expect all of her excretory mechanisms to be impaired sufficiently to induce an acidosis; however, on the second day of hospitalization the CO_2 combining power was 58.9 volumes per cent and on the ninth day after receiving ammonium chloride gr. 135 daily for four days (the morning after the greatest urinary output) the CO_2 combining power was 73 volumes per cent (done in duplicate). Thirteen days later with continued ammonium chloride therapy, the CO_2 combining power was 63.3 volumes per cent and the increased urinary output was maintained.

Case 4. (Table 1) O. R., female, aged 51, was admitted for the second time within seven months complaining of shortness of breath, cough, blueness of the face after coughing, pain over the heart and swelling of the ankles. Upon physical examination the patient was found to be markedly obese (weight 233 lbs.), slightly cyanotic, and orthopneic. The chest was dull on percussion over both bases and moist râles were present. The heart was enlarged to the left. The pulse rate was 120; blood pressure 160 systolic and 100 diastolic. The abdomen was extremely obese. Ankle edema was graded one plus.

This patient received ammonium chloride gr. 135 daily beginning the twenty-seventh day of hospitalization. After eight days of ammonium chloride medication the CO_2 combining power was 49.2 volumes per cent and after 16 days it was 52.2 volumes per cent. A mercurin suppository resulted in a marked diuresis on this day.

Case 5. (Figure 2) T. M., male, aged 51, had nocturnal cough for several months and these "asthmatic attacks" had been increasing in severity. For the past month he had been forced to use three pillows and was very short of breath upon the slightest exertion. He was conscious of his heart pounding with an occasional pronounced thump. His legs had been swelling for about six weeks. For the past two weeks he had had a sense of fullness in his upper abdomen which was most distressing. The patient was observed to be orthopneic and dyspneic. He had dullness and râles over both bases. His heart was enlarged to the left and was totally irregular in rhythm. There were no murmurs. The apex rate was 114 and the blood pressure 146 systolic and 76 diastolic. His liver was enlarged downward and tender. Sacral and ankle edema were graded three plus.

This patient received 1 c.c. of salyrgan intravenously on the first day which resulted in a very mild diuretic response (figure 2). After digitalis

and ammonium chloride therapy, however, excellent results were obtained with both mercurin suppository and intravenous salyrgan. In both these latter instances larger doses of the mercurials were given. In this case there also was a slight rise in the CO_2 combining power in the face of continued use of ammonium chloride, gr. 90 daily. This observation was constant in the three cases in which these determinations were made.

Ethridge et al.[8] found in studying the effect of inorganic salts on the diuretic action of salyrgan that the acidifying salts caused an increase in diuresis. They observed a moderate decrease in the CO_2 combining power

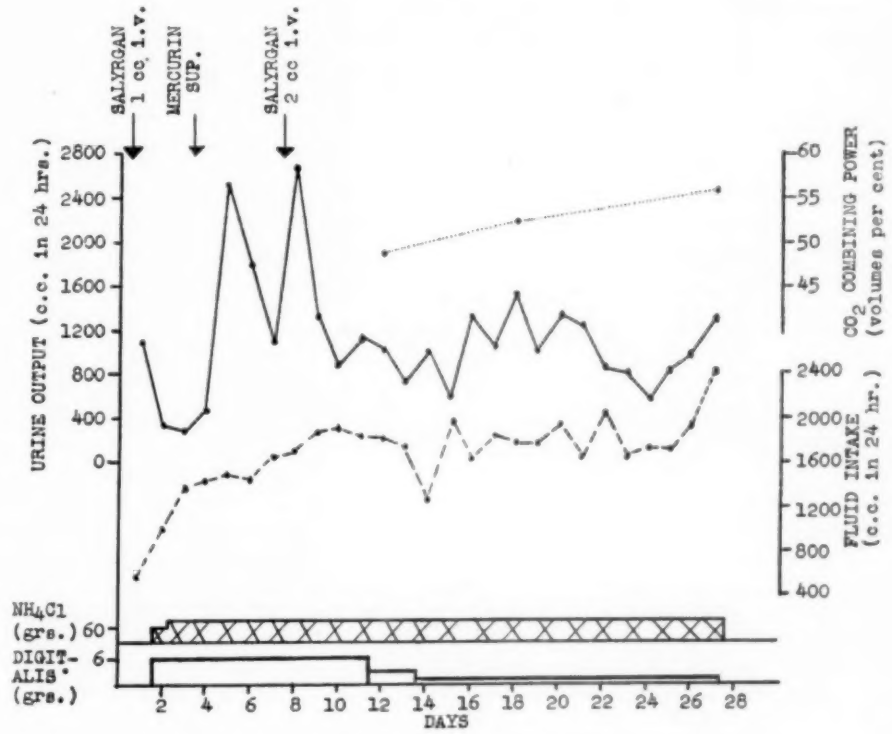

FIG. 2. *Case 5.* Aged 51, M. Arteriosclerotic heart disease.

of the plasma of dogs three hours after the administration of ammonium chloride by stomach tube. They attributed the enhancement of the diuresis to this moderate acidosis.

Dennig et al.[9] observed that patients who took large amounts of ammonium chloride daily developed a greater degree of acidosis on the second and third days of administration than subsequently even though the ingestion of the salt was continued.

Keith[10] feels that the change in the CO_2 combining power is not of sufficient magnitude to account for the increase in diuresis when the acid

forming salts are given. He believes that the specific action of the acid radical is an important factor.

The findings reported in this protocol tend to minimize the importance of reduction of the CO_2 combining power.

Case 6. (Figure 3) A. H., male, aged 62, had first noted shortness of breath six months prior to admission. Because of this complaint he had been forced to

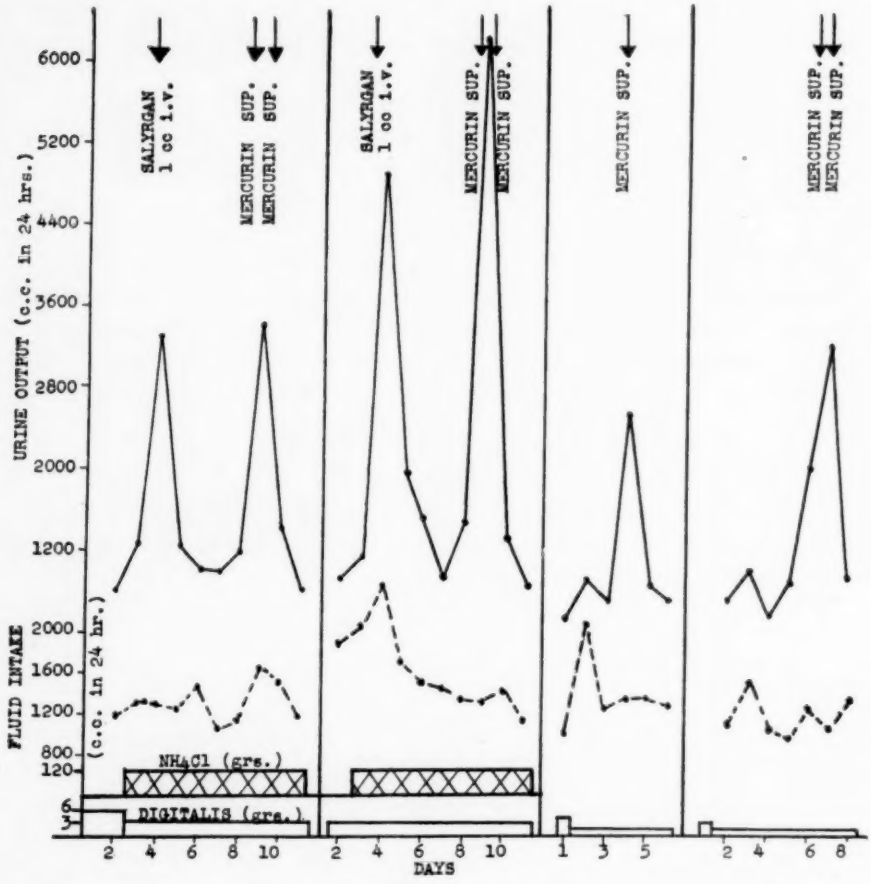

FIG. 3. *Case 6.* Aged 62, M. Syphilitic and arteriosclerotic heart disease.
Case 7. Aged 30, M. Hypertensive cardiovascular disease.
Case 8. Aged 67, M. Arteriosclerotic heart disease.
Case 9. Aged 61, M. Arteriosclerotic heart disease.

limit his activity but despite this care his dyspnea became more severe. He had noticed edema of the ankles for two months. He had consulted his physician at the start of his complaints and the doctor had told him that his blood pressure was "195." The patient stated that at times he had spots before his eyes and roaring in his ears.

The patient was not acutely distressed. Upon examination a bony growth was found on the hard palate. His teeth were carious and the gums were infected. His

tonsils were enlarged. Râles were heard over the bases of both lungs. The heart was enlarged to the left and the apex rate was 110. The blood pressure was 190 systolic and 120 diastolic. The abdomen was obese and edema of the ankles was present, graded two plus. The blood Wassermann test was four plus on two occasions. Fluoroscopy revealed a diffuse dilatation of the aorta.

Case 7. (Figure 3) P. M., male, aged 30, first noticed shortness of breath one year prior to admission. He had been put to bed for 14 weeks. Digitalis was administered, but was discontinued when he was allowed to leave his bed. For the three weeks preceding admission he had suffered epigastric fullness, belching and constipation. He had a mild cough which caused pain in the right upper quadrant.

When observed the patient was sweating profusely although not in acute distress. He was moderately obese. Râles were present in both bases posteriorly. The heart was moderately enlarged to the left; the pulse was 115; gallop rhythm and an occasional extrasystole were noted. The blood pressure was 165 systolic and 135 diastolic. The abdomen was moderately obese and the edge of the liver was definitely palpable and quite tender. The lower margin of the spleen was felt at the costal margin. Edema of the lower extremities and over the sacrum was of moderate grade.

In case 5 (figure 2) and cases 6 and 7 (figure 3) a comparison between the efficacy of mercurin suppositories and intravenous mercurials may be drawn. An approximately equal degree of diuresis was obtained with each method, but a greater amount of mercury was administered in the suppositories.

Case 8. (Figure 3) H. M., male, aged 67, was brought into the hospital acutely ill with orthopnea and cough. He had had "bronchitis" for years, but, several weeks before, he complained of a moderately severe, non-radiating pain over the heart which had persisted for several days. Following the pain the bronchial symptoms became worse. On the night of admission the patient had a severe seizure of coughing with production of pink, foamy sputum and marked shortness of breath. His face became cyanotic and he appeared in great distress. The chest was emphysematous with a precordial bulge. Wet, rattling râles were present throughout both lungs. The heart was enlarged to the right and left; the rate was 120 and the rhythm totally irregular. The blood pressure was 130 systolic and 70 diastolic. The liver edge was palpated 4 cm. below the costal margin and was not tender. There was no edema. The patient responded promptly to venesection and stimulants. An electrocardiogram showed auricular fibrillation, and premature ventricular contractions; evidences of coronary occlusion were present. Fluoroscopic examination revealed a greatly enlarged heart and a diffuse, almost aneurysmal dilatation of the aorta. The blood Wassermann was repeatedly negative.

Case 9. (Figure 3) I. M., male, aged 61, complained of difficulty in breathing. He was a known mild diabetic and had had hay fever and "asthma" for 15 years. For the past year he had experienced gradually increasing weakness, dyspnea, and swelling of his ankles. Also he had complained of belching for the past three months. The patient was obviously dyspneic and coughed frequently. Fine râles were heard over the right side of the chest but no asthmatic wheeze was apparent. The heart was enlarged to the left and the tones were distant and muffled. An occasional extrasystole was present. The pulse was regular, rate 100; blood pressure 114 systolic and 70 diastolic. The abdomen was negative except for the liver which was easily palpated. Pitting edema was found upon examining the extremities. The diabetic state was found to be under control. The chest signs and respiratory symptoms disappeared in response to cardiac therapy.

Case 10. (Table 1) E. M., male, aged 44, stated that he had had an attack of rheumatic heart disease at the age of 35. At that time he had shown all the symptoms and signs of cardiac decompensation and had been told that he had murmurs. Later he was informed that his recovery was complete. A few weeks prior to his admission he had a mild cold which was followed by pounding of the heart, shortness of breath, and swelling of the extremities. The patient showed marked pallor, dyspnea and orthopnea. Râles were present throughout both lungs. The heart was enlarged to the left. Pulse rate was 140, rhythm totally irregular. The blood pressure was 135 systolic and 65 diastolic. The liver was palpable and tender. Extremities were edematous. No petechiae were found. The temperature was 101° F. by rectum. An electrocardiogram proved the cardiac irregularity to be auricular fibrillation.

The urinalysis of this patient on admission yielded findings typical of chronic passive congestion: Specific gravity 1.020, albumin plus, 3–5 red blood cells per high power field (centrifuged). A mercurin suppository was given on the second day but the patient showed only a slight, if any, increase in urinary output and this questionable increase was delayed until 48 hours after the administration of ammonium chloride had been begun. A second mercurial suppository was given on the ninth day, and 48 hours after its administration (and six days of ammonium chloride therapy) the patient suddenly became disoriented, had thick speech and hyperpnea. He complained of double vision, and there was paralysis of the fourth cranial nerve. He was thought to have had a cerebral embolus. The urine the next day contained innumerable red blood cells; gross hematuria continued for a month and microscopic hematuria persisted until the patient's death. The patient had a rising blood pressure from 135 systolic and 65 diastolic to 184 systolic and 85 diastolic; a rising azotemia up to a level of urea nitrogen of 49 mg. per cent, and of non-protein nitrogen of 75 mg. per cent. The urea nitrogen to non-protein nitrogen ratio was 0.65. The blood cholesterol dropped from 185 mg. per cent to 155 mg. per cent; the CO_2 combining power at the time of the acute episode was 29.6 volumes per cent. The specific gravity of the urine on 22 separate specimens ranged between 1.010 and 1.016. The anemia increased. The blood chemical data and the urinary findings at this time pointed to rapidly contracting kidneys such as are found in a fulminating type of diffuse glomerulo-nephritis. An intravenous urogram two weeks prior to death was unsuccessful because of inadequate concentration of the dye in the kidneys. The auricular fibrillation persisted as did the diplopia and the thick speech. The patient died 10 weeks following the first cerebral embolus. He complained of headache, lapsed into coma with stertorous breathing, hyperreflexia, increase in edema and multiple petechiae on the lower extremities. (These were the only petechiae ever observed during the patient's entire illness.) The patient died 24 hours later. Permission for autopsy was denied but the cause of death was thought to be a second cerebral embolus.

Keith [10] pointed out that hematuria and renal insufficiency has occurred, though rarely, from the injection of organic mercurials. He also observed that ammonium chloride may induce a mild renal insufficiency which is usually temporary in duration.

Case 11. (Table 1) T. C., male, aged 33, had been a known luetic for 12 years. Six weeks prior to admission the patient had received the last of 12 doses of arsphenamine. For the 10 days preceding admission the patient complained of an increasing yellow tinge to his skin and of vague abdominal pain.

Physical examination was negative except for marked icterus and slight tenderness in the right upper quadrant. Chemical studies supported the history by indicating the presence of a toxic hepatitis. In the second week in the hospital the

patient complained of a distended abdomen and by the eighteenth day free fluid was detected. During the third week the patient called attention to discomfort in his rectum. Following the onset of the ascites, he had developed large, tender hemorrhoids.

Case 12. (Table 1) G. G., male, aged 58, had had pain in the upper abdomen for two months. The pain was not severe but annoying, and his "asthma" which he had had for several years became increasingly worse. He also had been aware of increase in his abdominal girth and his legs were markedly swollen. The patient's face was covered with spider telangiectases and it also had a slight icteric tinge. Râles were present throughout the chest. The heart was enlarged to the left and a systolic murmur was heard over the entire precordium. The pulse rate was 92 and regular; the blood pressure was 155 systolic and 85 diastolic. There was an umbilical hernia present and the abdomen was distended with fluid. The liver was firm, non-tender, and palpable on ballottement. The lower extremities were markedly edematous. The patient had large, tender, protruding hemorrhoids. During the course of treatment the râles and edema disappeared in response to cardiac therapy but the ascites increased. Frequent paracenteses were of only transient aid. The patient developed a psychosis during his illness with paranoid manifestations. Chemical studies revealed an icteric index ranging from 14 to 30; normal figures were found for urea nitrogen, amino acids, non-protein nitrogen and cholesterol. The cause of the persistent ascites was considered to be hepatic cirrhosis. The patient's course was downhill in spite of all therapy. Permission for autopsy was denied.

In cases 11 and 12 (patients with hepatic cirrhosis, ascites and hemorrhoids), the suppositories caused discomfort because of the rectal lesions. In case 11 the suppositories were expelled within 20 minutes because of the local distress. In this case, however, there was a diuresis but it may have resulted from the ammonium chloride which the patient also was receiving. In case 12 mercurin suppositories on four occasions failed to result in diuresis. Intravenous injection of 2 c.c. of mercupurin caused no increase in urinary output in one instance but on a subsequent injection an output of 2,050 c.c. was obtained. This patient was quite refractory and refused ammonium chloride in solution or as enteric coated pills. The ascites in cirrhosis cases does not respond well to mercurials intravenously and with impaired absorption and brief time of retention of the suppositories it is not surprising that the rectal route of mercury administration was not efficacious in these two cases.

Summary

Mercurin suppositories were used on 20 occasions in 10 patients with varying degrees of cardiac decompensation. These patients were routinely treated by bed rest, sedation, digitalis and restricted fluid intake. In 17 instances (85 per cent) a diuresis ranging from 1,950 c.c. to 8,750 c.c. in 24 hours resulted from the use of the suppositories. In one of the failures (case 2, table 1) the diuresis was delayed following the suppository administration until the third day of ammonium chloride therapy. The other two failures were obtained in case 10 (table 1) which showed renal complications. Renal insufficiency followed the mercurial suppositories and

ammonium chloride administration in this case but the subsequent death apparently was caused by a cerebral embolus.

In the two cases of hepatic cirrhosis studied, mercurin suppository did not seem to be the best form of mercury administration because of the rectal discomfort and the lack of consistent increase in urinary output.

Conclusions

1. The mercurin suppository is an effective diuretic agent in selected cases.

2. It is most efficacious when used in conjunction with ammonium chloride. Ammonium chloride is a valuable adjunct and in some cases essential to the production of a satisfactory diuresis. In three cases in which the CO_2 combining power was observed at intervals, ammonium chloride had a marked synergistic diuretic effect even though normal or elevated CO_2 combining powers were present.

3. Mercury is a renal irritant and its use in any form should be carefully controlled by frequent urinalyses.

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SOME PUBLIC HEALTH ASPECTS OF UNDULANT FEVER *

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IN this brief discussion undulant fever is treated as a public health problem in order to bring out a few points concerning the diseases in lower animals from which the human being derives his infection. It is felt that to many medical men more information concerning the manifestations of this disease in domestic animals will be of interest.

Considerable confusion exists over the terminology. Malta fever, undulant fever, brucellosis, brucelliasis, Mediterranean fever, Bang's disease and many other terms are employed. Similarly there has existed among bacteriologists considerable controversy over the classification and relationship of the bacteria present in the lower animals afflicted with this disease or group of diseases.

For practical purposes there seems to be enough agreement to permit calling this entire group of fevers the brucella group, reserving the term undulant fever for the clinical disease seen in man, which is apparently the same disease regardless of the source of infection. Similarly, there is considerable agreement as to the classification of the three main species of bacteria etiologically responsible. These are: *Brucella melitensis* causing Malta fever in goats; *Brucella abortus* causing contagious abortion in cattle, and *Brucella suis* producing abortion disease in swine. As previously stated, infection with any of these three results in undulant fever in man and the disease appears to be the same regardless of its source.

Experimentally brucella infection can be produced in any warm blooded animal, but the three diseases mentioned above are the only ones with which we need be seriously concerned.

In America the milch goat can be dismissed as being a very minor factor in the spread of undulant fever, although a few cases have been traced to imported goats, and several years ago a serious outbreak occurred in the southwest where European goats had been introduced on a fairly large scale commercially.

Granting that this source is a minor one, the history of Malta fever is too interesting and has added too much to our knowledge of brucellosis in general to be disregarded completely. (Incidentally, the term Malta fever was objected to so strenuously by the Maltese that the League of Nations Health Organization changed the name to undulant fever in their official list of diseases.)

The fever has been known for centuries in Mediterranean countries. In fact Hippocrates described a fever which historians now recognize as being Malta fever. During the eighteenth and nineteenth centuries various accounts of the disease appeared and during the Crimean war considerable confusion existed due to the simul-

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taneous presence of Malta and typhoid fevers in the British troops. The disease was first found to have a specific etiology in 1886 when Colonel Bruce [1] described a small cocco-bacillus seen in sections of spleen and the following year isolated the bacillus from human cases found on the island of Malta. He seems to have been the first to name the organism *Micrococcus melitensis.*

The next big step in studying the disease took place in 1897 when Wright and Semple [2] showed that it could be diagnosed by agglutination with the blood serum of infected animals.

In 1904 a commission was appointed by the British admiralty, the war office and the civil government of Malta to study the problem. Among their most important findings may be listed the fact that over 40 per cent of the goats on the Island of Malta were infected and that a big percentage of these were eliminating virulent bacteria in their milk. Human cases were traced to drinking such milk. Many other cases were found in herdsmen and those handling the infected animals. Many of these were found to have been infected through skin abrasions contaminated with urine from infected goats, in which large numbers of organisms were found.

In the commission's final report they stated that the most common method of infection in man was by the ingestion of infective articles of food, mainly milk.

When we come to consider contagious abortion in cattle and swine we find a more serious source of danger to man. This disease in animals has been reported from every civilized country and in America it has long since surpassed tuberculosis of cattle as an economic problem. It is this point of great prevalence which I wish to emphasize for I am sure it is not generally appreciated by the medical profession. We are accustomed to regard undulant fever in man as a comparatively rare condition and thus may lose sight of the fact that the possibilities for infection are almost unlimited.

The various states coöperating with the Bureau of Animal Industry are at present engaged in a vast control program which includes blood testing of large groups of dairy cattle. Without quoting any mass of data, I should like to give the figures for Missouri for the two year period ending October 31, 1936. Approximately 52,000 herds were tested in this state and infection was found in over 16,000 of them. Out of 640,000 cattle tested, 52,000 were found to be infected. These figures indicate in general what was found for the entire country in which over twelve million cattle were tested during this period and approximately one million reactors were found.

In a short discussion it is impossible to give more than a sketchy outline of the disease in cattle. Briefly the outstanding feature, as the name implies, is actual abortion in the gravid animal. The abortion is brought about by active inflammation within the uterus and the fetal membranes. A given animal may abort one or more times and then usually develops enough immunity to carry subsequent pregnancies to term.

Unless the uterus becomes invaded with other organisms which produce metritis and future sterility, actual illness is not apparent. The severe constitutional upsets seen in the human do not occur in either cattle, swine or goats. The bacilli live a more or less innocent existence within the body of the animal and are spread to the outside world in the lochial discharges

of the aborting animal, in the urine and feces, and through the milk where they appear continuously or in frequent showers. A microscopic mastitis without signs or symptoms is usually found in these animals. Rarely the male is found to react, the infection being present in the glandular systems, chiefly the testes. In cattle the disease spreads from animal to animal chiefly from contaminated pasturage or by means of infected food, the infection being spread chiefly by way of the gastrointestinal tract. The bacilli will remain alive and virulent for as long as four months in damp soil shielded from direct sunlight.

The disease in swine shows much the same clinical picture and needs no special mention.

Dr. Alice Evans [3] of the Dairy Division of the Bureau of Animal Industry was the first to point out the similarity between the *Micrococcus melitensis* of Bruce and the bacillus of contagious abortion first isolated by Professor Bernard Bang [4] of Copenhagen in 1897 and now usually called the Bang bacillus. She showed that the two are so similar as to be indistinguishable by ordinary laboratory means. Regardless of the source of infection, undulant fever runs the same course in man and routine agglutination methods will not suffice to determine which species is present. How recent is the knowledge that abortion disease in cattle could result in undulant fever in man is shown by a statement made by Dr. Evans in her 1918 article. In her discussion she states that "Since infection is dependent on the amount of infectious material, it may be that this difference in the number of bacteria in the milk of the two species of animals may account for our freedom from disease when cow's milk containing *Bacterium abortus* is consumed. On the other hand, are we sure that cases of glandular disease, or cases of abortion, or possibly diseases of the respiratory tract, may not sometimes occur among human subjects in this country as a result of drinking raw cow's milk?" This prophecy was made only 17 years ago and has proved only too true. We now know that brucella infection can and does attack every tissue and organ in the human mechanism. Ironically as it may seem, Dr. Evans herself was soon to prove how accurate her own surmise was.

Since such abundant opportunity to become infected exists, we may well ask why more cases are not reported. One reason I am sure lies in the fact that many cases are never diagnosed. Many of the cases which are diagnosed have been treated for other things first. This is especially apt to occur in communities where laboratory facilities for making serological tests are not easily available. The tendency of the infection to produce tender and swollen joints makes it easy to confuse with arthritis. Many cases start with the stepladder rise in temperature characteristic of typhoid. Chills with a daily rise in temperature are certainly suggestive of malaria and apt to be treated as such in the absence of proper blood examination. Another reason we do not see more of this disease is the fact that so much

milk consumed by the public is pasteurized. Proper pasteurization readily destroys the bacillus.

It is a well known fact, readily apparent clinically, that there is a great variation in the virulence of individual strains of the Bang bacillus found throughout the country. Occasionally a strain is encountered of such high virulence that practically every animal of breeding age in a herd will become infected and abort. At the other extreme is found a strain, isolated years ago by Huddelston, which he called an avirulent strain and which he used with impunity as a living vaccine in attempting to build up immunity in non-infected cows. This fact being true, whether an individual becomes infected probably depends to some extent upon how virulent a strain he encountered when the infected milk was consumed.

Infection with *Brucella suis* or the porcine strain is found chiefly in herdsmen, veterinarians, butchers and packing house workers who come into contact with infected animals or who handle the meat after such animals are slaughtered. In such cases infection probably enters through cuts and abrasions in the skin which have become soiled with the excreta of the living animal, or with the blood and tissue juices of the animals on their way through the various steps of packing house routine.

Undulant fever is diagnosed by the agglutination or complement fixation tests and by allergic skin reactions with culture filtrates such as the Brucellin of Huddelston. Cultural methods and guinea pig inoculation are valuable experimentally but too slow for routine clinical use. My own preference, based entirely upon tests in domestic animals, has always been for the complement fixation test in spite of its more involved technic. While it has now been practically discarded in favor of the much quicker and simpler agglutination test, I still have a feeling that it is the more accurate method. In man it is not uncommon to get a negative agglutination reaction on a patient known to be infected. In such a case the skin test will often be positive. On the other hand, positive agglutination does not always mean that the patient is actively infected. Some difference of opinion exists as to how low the dilution should be carried. Some laboratory technicians report any agglutination at all as being evidence of infection. In early work on Bang's disease in cattle, we disregarded agglutination in dilutions of $\frac{1}{50}$ or below as being false reactions. Ample clinical proof was available to support this stand.

It was formerly thought that agglutination in human serum might be due sometimes to ingestion of preformed antibodies present in milk since such antibodies are present in milk from practically all infected cows. This type of reaction has since been denied and the statement made that such antibodies cannot pass through the walls of the digestive tract. In this connection I should like to recall briefly an experiment I helped to conduct many years ago. We found routinely that just prior to calving most positively reacting cows lost their positive reaction and remained negative for

many weeks. The colostral milk at this time, however, was found to be almost unbelievably rich in immune bodies. It appeared that the protein fraction of the blood serum which carried these immune bodies had become concentrated in the colostrum and stored there. When these cows calved, if such calves were bled and tested immediately, before nursing their mothers, their serum always gave a negative reaction. If kept permanently from their mothers such calves could be raised by hand on other milk and reached maturity without ever giving a positive reaction. If, however, they were allowed to nurse, blood serum drawn two or three hours later always gave a strongly positive reaction. Similarly, calves from negative mothers, if given colostrum rich in antibodies, would show the same thing. Of course, the digestive tract of a young calf is entirely different from that of a man but it is hard to see how these newborn animals could ingest virulent infection and immediately develop enough immune bodies of their own to give strong serological reactions two or three hours later. It seems more logical to believe that preformed antibodies did pass through the intestinal wall barrier. If virulent cultures were given by mouth or hypodermically 10 or 12 days had to elapse before immune bodies could be detected in the blood.

In the matter of treatment the veterinary profession has practically run the gamut of drug and biological products with but scant success. Dean Giltner, previously quoted as being an outstanding authority, stated in a recent publication that "Curative treatment of brucellosis by the use of drugs or chemical has signally failed." All manner of bacterines, vaccines and sera have been used with occasional encouraging results but nothing has been devised which can be generally counted on for definite results. This therapeutic failure has greatly stimulated control programs which have for their goal the ultimate elimination of the disease by destruction of less valuable animals and isolation of those reactors too valuable to sacrifice. Healthy progeny can be raised from infected stock if removed from sources of contagion prior to reaching breeding age. By means of wholesale blood testing and proper sanitation it is hoped to establish accredited abortion-free herds and eventually to rid the countries' dairy and beef herds of this malady. Coöperation on the part of stock breeders will eventually be gained through necessity. Even now it is becoming practically impossible for a breeder to sell a pure bred animal without a negative blood test. Certified milk can be placed on the market only if the animals supplying it can be shown to be free from tuberculosis and abortion disease. Rigid restrictions against interstate shipment of infected cattle are now in existence in most states. Such restrictions have gone a long way to correct abuses which formerly existed. That such programs must go forward against tremendous odds goes without saying, but marked progress is being made.

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PROTAMINE–ZINC–INSULIN IN DIABETES*

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The observations reported in this paper were made in the management of 60 patients, some of whom had been treated with various preparations of protamine-insulin since February 1936. Since August 1936, all patients in this group have received protamine-zinc-insulin. Cases of all degrees of severity have been treated and four children are included in the group. The ages of the patients vary from 8 to 76 years.

It has been felt advisable to hospitalize all patients during the first part of their treatment. The hospital stay averaged 18 days. No patient was confined to bed except for some complication. An attempt was made in each case to maintain physical activity comparable to that of the patient's average day. During the hospital stay, venous blood was taken routinely for determination of the blood sugar at 8 a.m., 12 noon, 4 p.m., and 10 p.m. daily and in some cases at other hours in addition, a modification of the Myers-Bailey method being used. Twenty-four hour specimens of urine were collected in four periods daily, the periods ending before meals and at bedtime. Each specimen was tested for sugar by Benedict's qualitative method and when sugar was present, the 24-hour excretion was calculated in grams, Benedict's quantitative method being used. Qualitative estimation of ketone bodies was done on all urine containing more than 1 per cent glucose.

The Insulin

The protamine-zinc-insulin used in this investigation contained 40 units of insulin per cubic centimeter and approximately 0.08 mg. of zinc in combination with protamine in a buffered solution. Since the active material is present in fine particles, careful, gentle mixing is important before the withdrawal of each dose. The use of a cool, dry syringe is advised and it is recommended that subcutaneous injection be done in such a way as to insure a depot of precipitated insulin in the subcutaneous tissues. The material was supplied in 5 c.c. vials, each vial bearing the date after which its stability could not be guaranteed.†

The Diet

We have been accustomed to use a high carbohydrate, relatively low fat diet for some years and this practice has been continued. In our attempt to control diabetes of various degrees of severity with one dose of protamine-zinc-insulin, we have in some cases tended to be less rigid regarding the low

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† The protamine-zinc-insulin used has been generously supplied through the courtesy of Dr. F. B. Peck and the Eli Lilly Company.

level of fat which is usually maintained in such diets. The number of grams of fat per day in the routine diet was 60. It is our impression that a smooth control is more readily obtained when the carbohydrate content of the diet is not elevated above 200 grams per day. Some patients have received 250 grams of carbohydrate per day and the carbohydrate intake has been 175 grams per day or more in 42 of the patients. The average daily intake in the entire group has been: carbohydrate, 182 grams; protein, 66 grams; and fat, 75 grams.

The diet for each individual is calculated on the basis of the basal caloric requirement for ideal weight. In obese individuals, we have not usually found it advisable to use a daily caloric intake below such a figure, as this is usually considerably less than the basal caloric requirement for actual weight and thus produces a daily caloric deficit sufficient to maintain loss in weight where this is required. In most instances, the total caloric intake ranges between the basal caloric requirement for ideal weight and 40 per cent above it.

The diet has been divided routinely into three meals containing 30 per cent, 35 per cent, and 35 per cent respectively of the available glucose for the day. Considerable manipulation of this distribution is advantageous at times. With the use of protamine-zinc-insulin, it has not been found to be of frequent advantage to use one meal containing only 20 per cent of the daily available glucose as was advocated by Hagedorn, et al.,[2] and Root, Marble, et al.,[3] using plain protamine-insulin. In some cases we have divided the daily intake into four meals, giving a small proportion of the food as a luncheon at bedtime. This has the advantage of creating more even intake of food throughout the 24 hours and thus offsets to some degree the tendency to fasting hypoglycemia. In those cases in which there is an undue rise of blood sugar by noon, it is an advantage to deduct the food for the bedtime lunch from the regular breakfast.

Duration of Activity

Estimates of the duration of activity of a single dose of protamine-zinc-insulin in the human have been obtained from four types of observations:

1. The effect on the blood sugar level of a single dose given with one meal after which the patient is required to fast until such time as the blood sugar level tends to rise again after the action of the insulin is diminished. By such a procedure in mild cases, hypoglycemia can be maintained for a period extending to nearly 30 hours.

2. The number of hours during which blood sugar levels in a diabetic can be controlled by a single dose when the patient is receiving regular meals. This type of observation applies obviously to those cases in which the diabetes is of such a degree of severity that the blood sugars are almost but not completely controlled by diet alone.

3. The third type of clinical observation which indicates definitely that the insulin compound acts for more than a day is the commonly observed cumulative effect of daily doses over the first three days of its administration.

Figure 1 shows the effect of a single dose of protamine-zinc-insulin given at 7 a.m., at which time a breakfast of 45 grams of carbohydrate, 14 grams of protein, and 22 grams of fat was given after which the patient had no more food for 30 hours. The distinct fall in blood sugar levels is obvious in from three to six hours and subsequently the fall is gradual and consistent. The maximum effect is obtained 12 hours after administration. Hypoglycemia is maintained in this case to the twenty-seventh hour. In several observations of this type, the maximum effect appears in from 15 to 18 hours. Larger doses, however, may maintain hypoglycemia for a much longer time, as in Rabinowitch's [4] case in which a single dose of

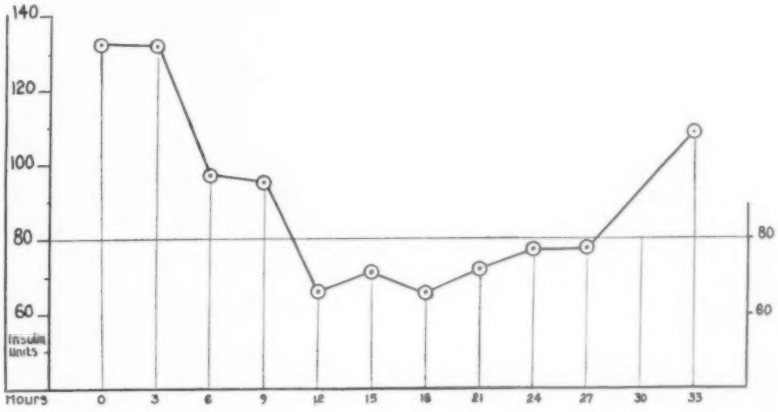

FIG. 1.

50 units of protamine-zinc-insulin maintained hypoglycemia for more than 36 hours.

The second type of observation mentioned is visualized in figure 2. In this patient, the diet which contained C. 100, P. 50, and F. 60, controlled blood sugar levels through the day except for the fasting levels which were 150 to 165 mg. per hundred cubic centimeters. A single dose of protamine-zinc-insulin was given on the morning of October 28. It will be noted on the chart that the fasting blood sugar levels were normal for two subsequent days, after which they rose to their original levels. Another single dose of protamine-zinc-insulin at that time controlled the fasting blood sugar levels for two more days.

The cumulative effect of daily doses of protamine-zinc-insulin is observed in nearly every instance in which the use of this material is begun. The maximum cumulative effect usually appears to be most marked on the third day and is most obvious in comparing the fasting blood sugar levels.

This appears to indicate that the dose given on the first of three days is still active to some degree on the third and also shows clearly why a reduction in dosage, as compared to regular requirements of insulin, usually is necessary.

Figure 3 shows the blood sugar levels in a case in which fairly satisfactory control was obtained with three doses per day of regular insulin, the doses being given at 8 a.m., 5 p.m., and 10 p.m. The first day depicted on the chart is a fairly typical representation of the previous control obtained, and it will be seen that the total required daily dose of regular insulin was 67 units. The patient had a mild afebrile infection of one great toe. She had been under control with regular insulin for two weeks prior to the use of protamine-zinc-insulin and had shown no significant alteration

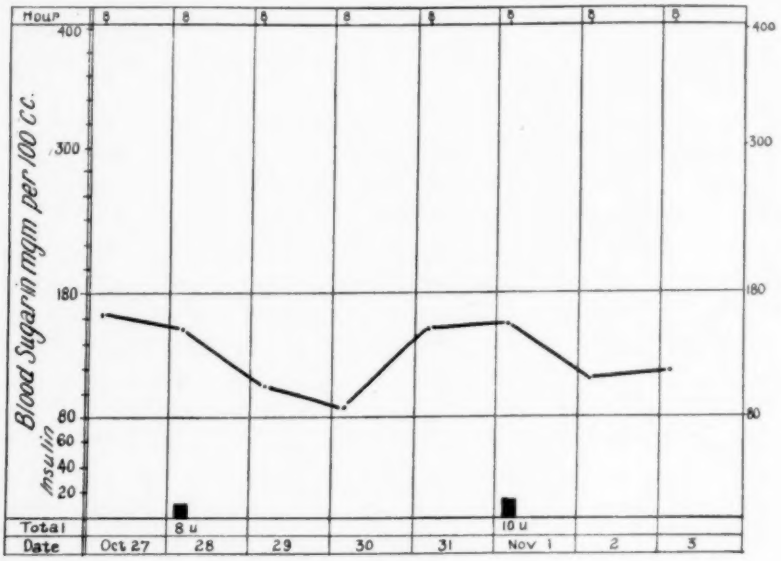

FIG. 2.

in necessary dosage. On the morning of November 3, 60 units of protamine-zinc-insulin were given in a single dose and this dose was repeated the following day. As will be seen, the fasting blood sugar level on the third day was distinctly lower than were those the first two days and on this day it was necessary to make an addition to the diet because of excessively low blood sugar levels. When the dose of protamine-zinc-insulin was reduced sufficiently to allow fasting levels to rise to the normal range, blood sugar levels during the day were not maintained at normal levels, indicating the necessity for an additional small dose of regular insulin. This patient was subsequently well controlled with a morning dose of protamine-zinc-insulin of 36 units, together with a dose of 6 units of regular insulin at noon.

The cumulative effect of a single matutinal dose of protamine-zinc-insulin may be shown by examining the average fasting blood sugar levels in a series of patients during the first few days of control with this insulin as compared with the average fasting blood sugar level preceding its ad-

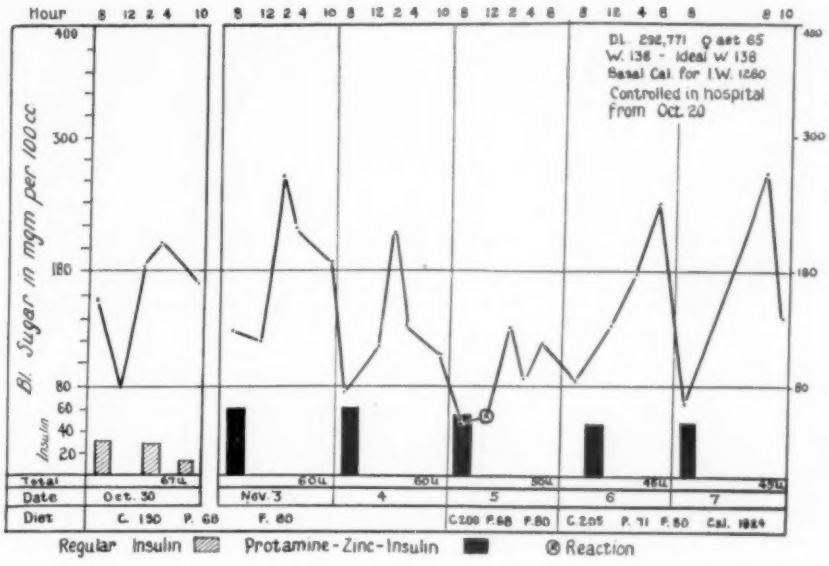

FIG. 3.

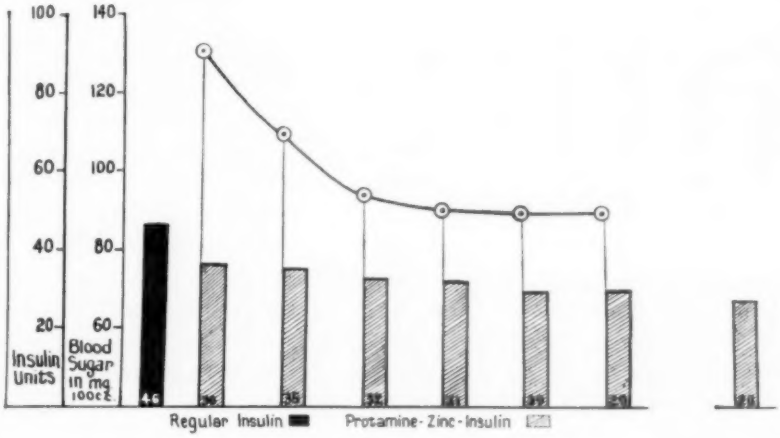

FIG. 4.

ministration. (Figure 4.) Fifteen cases were selected for this purpose. These patients were all under relatively recent control. The period of control with regular insulin in the hospital varied from 5 to 21 days and averaged 10.9 days before the first dose of protamine-zinc-insulin was given. During the period of regular insulin therapy, the diets were in-

creased in some of the cases but were at a fixed level for a period averaging 8.7 days. This dietary level was maintained throughout the period represented in the chart in all but one case in which it was raised because of insulin reactions. It was subsequently maintained at the new level.

The average reduction in total dosage of insulin is shown in the chart. In spite of the reduction in dosage, there was a distinct reduction in fasting blood sugar levels which was most obvious during the first three days. The detached block at the end of the chart indicates the amount of protamine-zinc-insulin necessary for control on the same diets at a period of from two to eight weeks later. As in other cases in the series, the reduction in dosage may fairly be ascribed in part to the fact that the patients had been under control for a short time only before the use of protamine-zinc-insulin. The fact that control was maintained in each instance on a dose suddenly reduced by about 20 per cent cannot, however, be explained on this basis and must be ascribed to the increased efficiency of the new insulin.

Number of Injections

Since the duration of activity of each dose of protamine-zinc-insulin is distinctly longer than 24 hours, there seems to be little or no advantage in giving more than one dose per day. A single dose per day usually is sufficient to control fasting blood sugar levels and the degree of depression of these levels apparently marks the limit of increase of the protamine-zinc-insulin dose.

Time of Injection

Although the duration of the effect of a single dose is longer than 24 hours, its effect is diminished in most instances after 18 hours. This being true, it seems advisable in most cases to give the single daily dose at a period longer than 18 hours prior to the low level of the day which usually is before breakfast regardless of the time of administration of the insulin. For this reason we have usually used the single daily dose before breakfast in each instance. In several cases in which the morning dose was shifted to before the evening meal, a further fall in fasting blood sugar levels was seen without any obvious advantage in control of the blood sugar levels during the day. In a few cases a second daily dose of protamine-zinc-insulin may be used to advantage and, in very severe cases, still better control may be obtained by supplementing one or both doses with regular insulin.

Estimation of the Dosage

In estimating the dosage of protamine-zinc-insulin, two chief factors must be borne in mind: (1) that the effect is cumulative as shown above, and (2) for this reason the total daily requirement must invariably be less than the regular requirement of insulin. Due to improvement in control, the required dosage may subsequently fall considerably. Where poor con-

trol is present and rapid improvement can be anticipated, this cumulative effect may be dangerous if it is not considered carefully.

Figure 5 shows the fasting blood sugar levels in a case in which control was poor while the patient was receiving 60 units of regular insulin per day. When the daily dose of regular insulin was raised to 80 units, the blood sugar levels fell somewhat but were still far above the normal range. Instead of first obtaining good control with regular insulin as we subsequently have found advisable, it was decided in this case to change to protamine-zinc-insulin, arranging a combination of protamine-zinc and regular insulin in such a way as to make the dose approximate 90 to 95 units per day. After the use of protamine-zinc-insulin for three days, the fasting blood

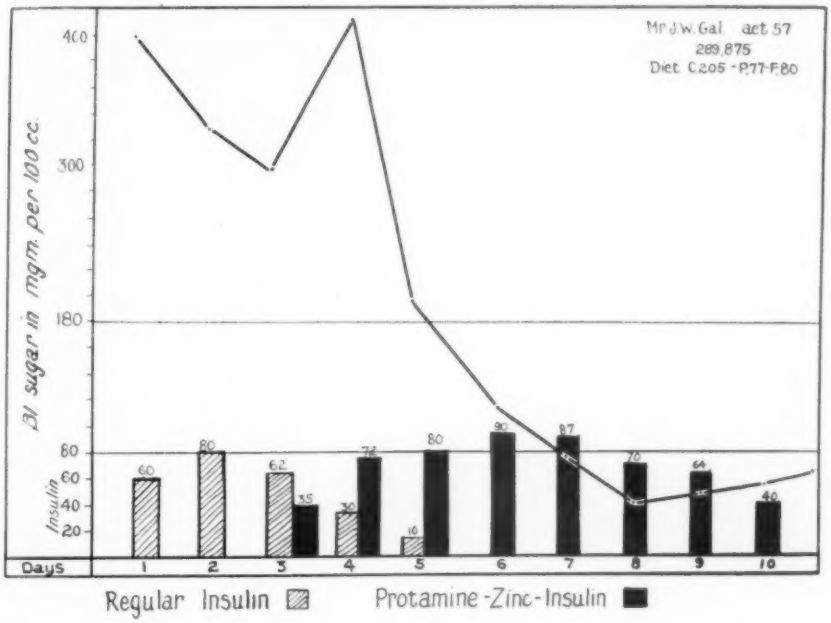

FIG. 5.

sugar levels had fallen to the normal range. The dosage was not reduced sufficiently at this time and the hypoglycemia which followed is apparent. It is interesting to note that no insulin reactions occurred. This case demonstrates the difficulty involved in estimating the proper dosage where good control is not obtained prior to the change from regular insulin to protamine-zinc-insulin.

When fairly stable control is first obtained with regular insulin, an immediate substitution with protamine-zinc can usually be made. However, we feel that the doses of protamine-zinc-insulin should seldom equal the doses of regular insulin and in cases of moderate severity it has been our practice recently to substitute a single dose of protamine-zinc-insulin of

about 80 per cent of the regular requirement of insulin. In the more severe case, considerable rise in blood sugar levels during the first few days is likely to occur. During this time, glycosuria is present but we have not seen acidosis of consequence during such a transition period. If the rise in blood sugar levels during the first two days of such a transition period tends to be excessive, it may be prevented by the addition of one or two doses of regular insulin which will not usually need to exceed more than 10 per cent of the previous requirement of regular insulin. Within a week, further reduction in insulin dosage is often necessary and in many of our cases even after leaving the hospital, further reduction may be found advisable within a period of two or three weeks.

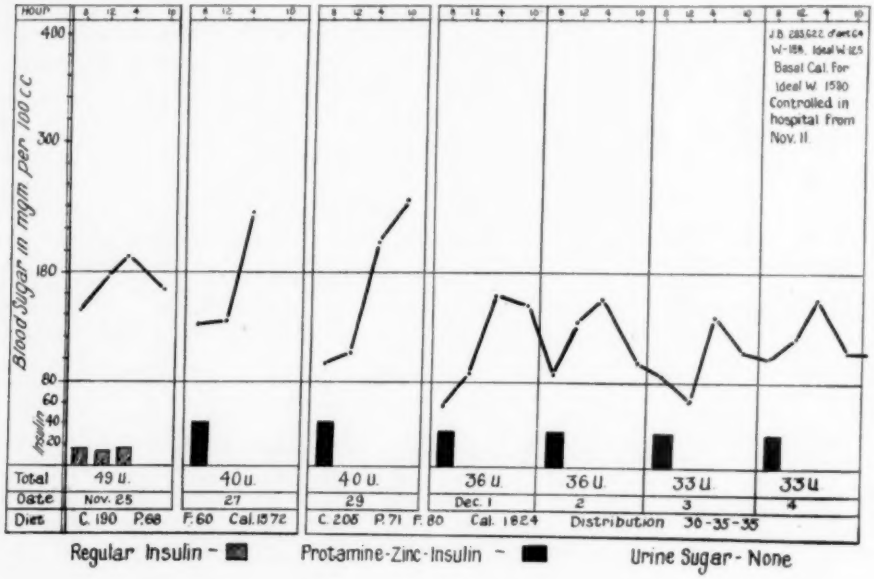

FIG. 6.

Figure 6 shows the blood sugar levels during a typical day of moderately good control with three doses of regular insulin, totaling 49 units. This patient was under control with regular insulin for 16 days prior to November 27. On November 27, 80 per cent of this dose, i.e., 40 units of protamine with regular insulin, was given as a single morning dose. The typical rise in blood sugar levels during the day for the first few days is apparent and the gradual fall in fasting blood sugar levels is also demonstrated. Subsequent reduction in dosage is shown and excellent control has followed the use of 33 units per day of protamine-zinc-insulin as compared to a less satisfactory control previously on 49 units per day of regular insulin.

Figures 7 and 8 show control for several days on diminishing doses of regular insulin, together with a smooth transition period and subsequent

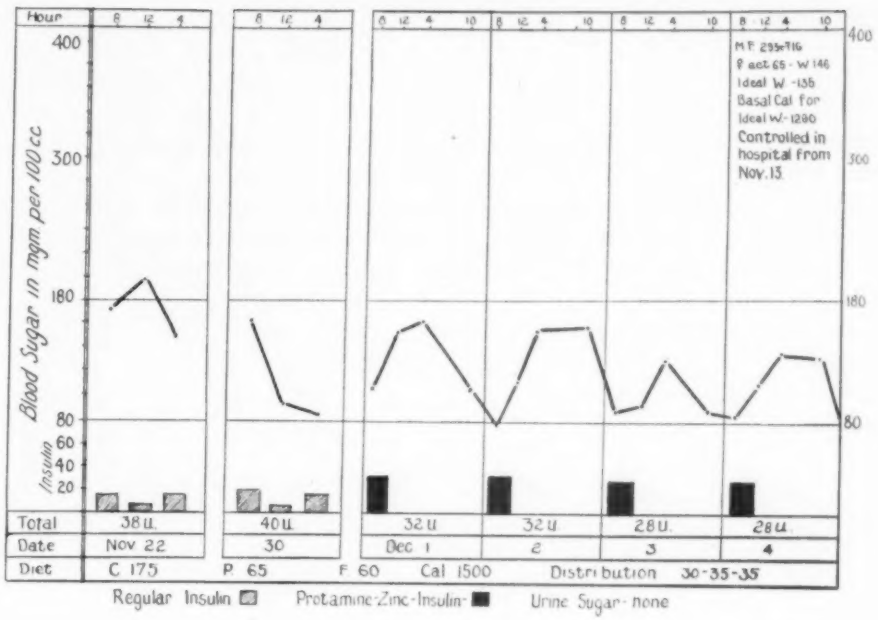
Hour
Blood Sugar in mgm per 100 cc
Insulin
M.F. 295-116
Ideal W -136
Basal Cal for Ideal W-1280
Controlled in hospital from Nov. 13
Total 38 u. 40 u. 32 u 32 u 28 u. 28 u.
Date Nov 22 30 Dec 1 2 3 4
Diet C 175 P 65 F 60 Cal 1500 Distribution 30-35-35
Regular Insulin
Protamine-Zinc-Insulin
Urine Sugar - none

FIG. 7.

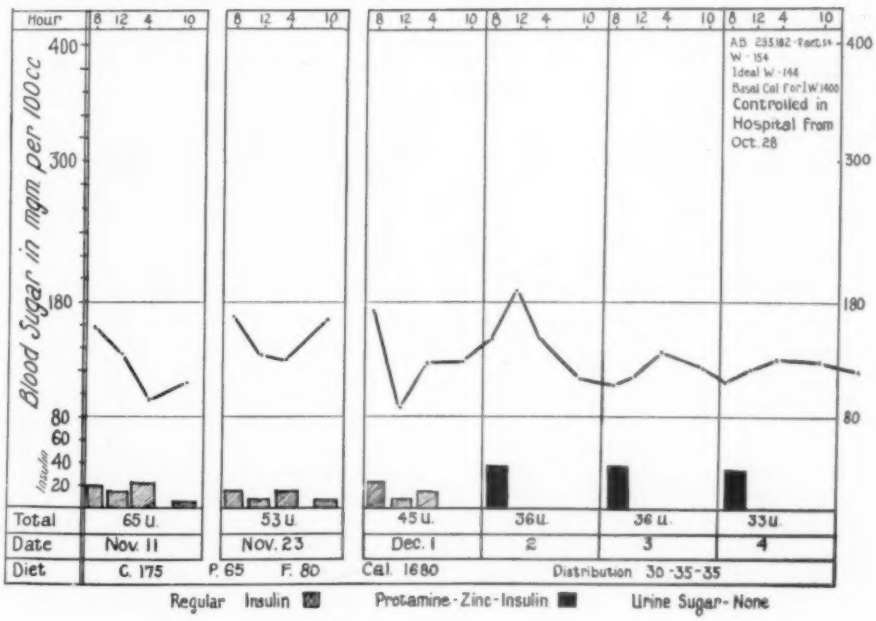
Hour
Blood Sugar in mgm per 100 cc
Insulin
A.D. 235-182 - Ideal W - 154
Ideal W - 144
Basal Cal For Ideal W 1400
Controlled in Hospital from Oct. 28
Total 65 u. 53 u. 45 u. 36 u. 36 u. 33 u.
Date Nov. 11 Nov. 23 Dec. 1 2 3 4
Diet C. 175 P. 65 F. 80 Cal. 1680 Distribution 30-35-35
Regular Insulin
Protamine-Zinc-Insulin
Urine Sugar - None

FIG. 8.

excellent control beginning with 80 per cent of the regular requirement of insulin with subsequent reduction in dosage.

As indicated above, in mild cases where only the fasting blood sugar level remains high, this can readily be controlled by daily single doses of protamine-zinc-insulin and such control can be accomplished by doses as small as 5 units per day.

Even in severe cases, the fasting blood sugar level will be the lowest of the day and, with sufficient dosage, it can be brought within normal range. If it is obvious, however, that the blood sugar levels during the day will not be controlled by such a dose, it will be necessary to add one or two doses of regular insulin. Such a case in which control was difficult is shown in figure 9.

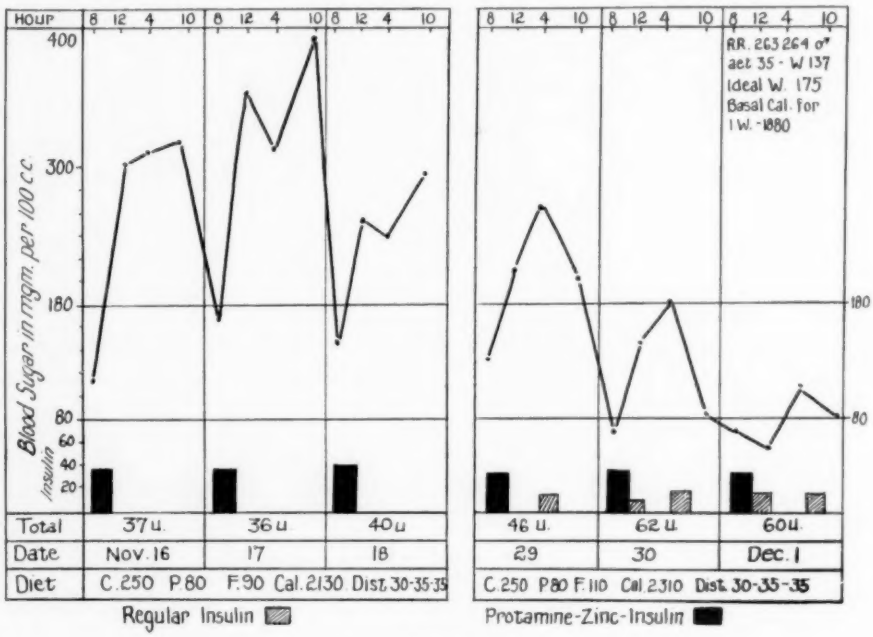

FIG. 9.

The general rules which we follow at present, therefore, in changing from regular to protamine-zinc-insulin may be summarized as follows:

The patient is placed on a well regulated diet and good control is obtained with regular insulin. An immediate change is then made with a single morning dose of protamine-zinc-insulin which is approximately 80 per cent of the previous requirement of regular insulin.

If the blood sugar levels during the day are excessively high, about 10 per cent of the previous requirement of regular insulin is added. The dosage of protamine-zinc-insulin is then manipulated in such a way as to

obtain relatively normal fasting levels, changes in dosage not being made oftener than every third day. Subsequently, if morning reactions occur and if the fasting urine is sugar-free or if the fasting blood sugar levels are excessively low for two successive days, a reduction in protamine-zinc-insulin is necessary. If, on the other hand, sugar appears in the morning urine and if the fasting sugar levels remain high for more than two consecutive days, the protamine-zinc-insulin dosage may be increased. Where the fasting blood sugar levels are well regulated, one or two additional doses of regular insulin will be necessary if the blood sugar levels during the day persist at abnormal heights.

Reactions

It is a remarkable fact that with the use of protamine and protamine-zinc-insulin, the blood sugar level may reach 40 mg. per hundred cubic centimeters or below without reactions. Reactions do occur, however, but for the most part they tend to be mild and gradual in their onset, thus allowing more time for treatment. Because of the gradual onset of such reactions, it is more difficult for the patient to detect an approaching reaction. Because of the prolonged effect of protamine-zinc-insulin, the reactions themselves are likely to be prolonged and to recur after treatment. Considerable hypoglycemia may occur without pronounced symptoms. It becomes more necessary than ever, therefore, to elicit any symptoms or signs which may be evidences of hypoglycemia. This is especially true in elderly individuals or in those with arteriosclerosis, especially arteriosclerotic heart disease. Fatigue, tingling, slight disturbance of memory, irritability, slight difficulty in speech, mild nausea, or headache should be suspected as possible symptoms of hypoglycemia. I have seen three severe reactions. One was associated with a convulsion, and this occurred in a child whose symptoms of hypoglycemia were present in this instance for nearly 12 hours. One occurred in a patient with severe diabetes which required 70 units of insulin per day. This patient lay down to rest after breakfast and was unconscious until he was awakened and found to be in obvious hypoglycemic shock at 5 a.m. the following morning. (He went to work as usual that day.) The third patient took 50 units of insulin instead of 25 as ordered.

In the treatment of protamine-zinc-insulin reaction, it is advisable to use small doses of glucose or milk, to be prepared to repeat the treatment if necessary, and to avoid the use of excessively large amounts of sugar at one time.

Reduction in Dosage and in Number of Injections

In 17 patients in this group, previous control had been good and had been maintained at a relatively stationary level for more than six months preceding the use of protamine-zinc-insulin. The average daily requirement of regular insulin had been 34.3 units while that of protamine-zinc-insulin was 22.0 units. In the older and better controlled cases, the reduction in

dosage is less than in the recently controlled cases. Of the entire group, the daily dose dropped from an average of 42.3 units of regular insulin to 25.4 units of protamine-zinc plus regular insulin.

Accessory regular insulin was necessary in 17 cases. The average number of daily injections necessary in the whole group was 2.8 of regular insulin as compared with 1.3 of protamine-zinc. This difference appears to be increasing with experience since, in the last 28 patients treated, the use of accessory regular insulin has been found necessary in only two instances. The average daily number of injections in this smaller group was 3.0 of regular insulin and 1.1 of protamine-zinc-insulin.

Contraindications

The usually recognized contraindications are acidosis, infections, and pre- and postoperative care. Attempts are being made to determine the usefulness of protamine-zinc-insulin in these conditions but experience is not sufficient to warrant comments.

Comments

Since the appearance of Hagedorn's paper in January 1936[2] his original claims that it had a prolonged action, gave better control in most cases, a tendency to less frequent insulin reactions with a diminishing number of injections and a reduction in actual dosage have largely been corroborated by other investigators.[3, 4, 5, 6] More recently, the addition of zinc to protamine-insulin has received considerable attention and it appears that the use of protamine-zinc-insulin has superseded that of plain protamine-insulin.

Although the advantages of protamine-zinc-insulin outweigh its disadvantages, the latter have not received sufficient emphasis. Better control can be secured with it in many cases but regulation, especially in the severe cases, is more difficult and will require a more intelligent grasp of the problem by the physician than has been necessary previously.

The comparative effectiveness of protamine-zinc-insulin should not be judged by blood sugar levels alone since, in some instances, it can be shown that even though the blood sugar levels fasting and four hours after meals are in good control, there may be more glycosuria than when the same levels are maintained with regular insulin. This appears to be due to the absence of the timely effect of insulin seen where regular insulin acts approximately synchronously with food absorption, as compared to the absence of this effect with protamine-zinc-insulin. It is remarkable that such increased glycosuria occurs infrequently.

Hospitalization for control is more important when protamine-zinc-insulin is used and usually will be more prolonged. Although reactions are less frequent, if they do occur, they are likely to be more difficult to detect and more prolonged.

In some of my cases reactions have occurred because the patient, having

taken a relatively large dose of protamine-zinc-insulin in the morning, has been unable to take all the food prescribed or has vomited part of the noon or evening meal. With regular insulin one would have the opportunity of reducing the noon or evening dose but this cannot be done with protamine-zinc-insulin. What effect this will have on the patient with arteriosclerosis remains to be seen. Some of the early disadvantages, such as instability of the solutions and the necessity of mixing them, have already been overcome.

Against these disadvantages we have more stable control, fewer injections, and lower dosage with protamine-zinc-insulin. It is hoped that, as a result of the better control, there will be a diminution in the incidence of hyperlipemia, liver disease, and degenerative disorders, especially arteriosclerosis. In these respects, the responsibility of the profession has increased.

Summary

Protamine-zinc-insulin in common dosage appears to be active for 50 to 65 hours after injection. Its maximum effect is usually maintained between 12 and 18 hours. The prolonged effect of single daily doses makes it unnecessary usually to use more than one dose daily. The cumulative action increases to the third day or longer and reduces the requirement of insulin to less than 75 per cent of the dose of regular insulin in most cases. The number of injections, dosage, and the frequency of reactions are all reduced by its use. The most obvious advantage is in reduction in number of doses necessary. In all except two cases in which we have used it thus far, control has been as good or better than with regular insulin. It should be pointed out, however, that this improved control represents in some cases the combined use of protamine-zinc-insulin and of regular insulin. A normal fasting blood sugar level marks the limit of increase in protamine-zinc-insulin dosage. If, when this limit is reached, the blood sugar levels during the day remain high, one or more accessory doses of regular insulin are required for control. In some mild cases, a dose of protamine-zinc-insulin every second or third day may be sufficient to control fasting sugar levels.

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THE ASSOCIATION OF SCIATIC NEURITIS WITH LIVER DISEASE *

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PERIPHERAL neuritis occurs commonly in metabolic disorders such as gout and diabetes. In severe anemia, renal and hepatic diseases, on the other hand, the central nervous system is more frequently involved. Lenticular degeneration has been described in association with cirrhosis of the liver.[1] Involvement of the peripheral nerves may also complicate liver disease. Polyneuritis has been ascribed to jaundice independently of a basic vitamin deficiency or alcohol abuse,[2] and also it has been thought due to the severe liver damage of biliary obstruction.[3] Neuritis has been noted in subjects with pigment cirrhosis, particularly in those with involvement of both the pancreas and liver.[4] Endogenous toxic substances resulting from hepatic insufficiency have been held responsible for causation of the neuritis.

This report of five cases indicates that the symptoms of sciatic neuritis in some instances may be a precursor of hepatic insufficiency. Though an analgesic effect of hepatitis and jaundice upon sciatic pain has been noted, the possible relationship between the jaundice and the antecedent sciatic pain has escaped notice.[5] Such a relationship may be important, for the development of jaundice, sometimes fatal, has recently been ascribed to the use of cinchophen prescribed for its analgesic effect.

The following clinical observations suggest that sciatic neuritis may be an early manifestation of a disease process which may lead to liver disease and hepatic insufficiency. It is suggested that endogenous or exogenous toxic agents may affect peripheral nerves before their hepatic effects become manifest clinically.

CASE REPORTS

Case 1. B. M., 48 years old, complained of bloating, belching and intolerance to fatty and fried foods of many years duration. For 18 months he had suffered a sensation of epigastric discomfort after meals. For six months he had suffered progressively more severe, cramp-like pains shooting down the posterior aspect of his left buttock, thigh, and calf. At times, only a feeling of numbness or discomfort existed. A month before admission to the hospital, the patient developed jaundice, darkly colored urine and clay-colored stools. He complained of generalized itching. His appetite failed him. He lost 10 pounds in weight. The only medication ingested by the patient throughout the course of his illness before admission to the hospital was ten grains of aspirin. With the onset of jaundice the pain in the left lower extremity became milder but did not disappear.

An enlarged, smooth, firm liver and an enlarged spleen were found on examination of the abdomen. Neurological examination revealed negative Patrick

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and Lasègue signs in the extremity affected with pain. The ankle jerk was present. The blood Wassermann reaction was negative.

Ascites and dependent edema developed. The patient lapsed into stupor and died despite intensive intravenous glucose therapy.

Necropsy confirmed the clinical diagnosis of subacute liver atrophy. The gall-bladder was normal in appearance and contained no stones. There was little evidence of hepatic regeneration microscopically. The pathological picture was also interpreted as a form of toxic cirrhosis. Unfortunately material was not obtained from the sciatic nerve in this case, or in case 4, for histological examination.

Case 2. S. M., aged 52 years, had received anti-luetic therapy. The last course of salvarsan had been administered five years before the hospital admission for diagnosis as to the cause of jaundice. For three weeks before the development of jaundice, the patient had suffered from severe pain in the posterior aspect of the right knee and thigh. Cinchophen had not been ingested.

The liver was enlarged and the spleen was not palpable. On neurological examination all reflexes were normal. The Kahn test was 3 plus.

The jaundice disappeared promptly. The sciatic pain subsided with the onset of the jaundice. The patient was ambulatory during his illness. In the four years since this illness, the patient has suffered no recurrence of sciatica.

The jaundice was classified as a so-called "catarrhal jaundice." In view of the fact that five years had elapsed since the administration of salvarsan, arsenic from this source was not considered in the etiology of the jaundice or sciatic neuritis.

Case 3. W. M., a physician, aged 45 years, had taken novatophan 18 years previously for severe sciatica. He had recovered from an attack of paratyphoid fever the year before. Splenic enlargement had been first noted 17 years ago, and liver enlargement had been known to exist for 14 years. For two years, left-sided sciatica had been present intermittently. Cinchophen had not been taken in recent years. For two weeks he had noted nausea and fever, and following this jaundice became evident. The sciatic pain subsided.

The liver and spleen were enlarged, and the laboratory tests indicated severe liver damage.

The patient ran a fever at the outset. Generalized itching was pronounced at times. After a protracted course, the jaundice subsided. The sciatic pain recurred after the acute phases of the illness had passed. It was believed that the patient has recovered from an attack of acute hepatitis superimposed upon an old toxic cirrhosis.

Case 4. R. B., aged 57 years, was admitted with a history of pain down the left thigh and leg of sudden onset and of eight weeks duration. After four weeks of pain of increasing severity, the patient had sought medical relief. She had been given six subcutaneous injections of Aolan, a milk preparation, and one intravenous injection of sodium iodide, without relief from pain. A single injection of 5 grains of cinchophen was then administered by a physician. One week later she developed icterus, anorexia, and epigastric distress. The stools became light in color. The sciatic pain definitely subsided with the onset of jaundice.

The liver was found enlarged, the spleen was not palpable. The Patrick and Lasègue signs were positive in the left lower extremity. The knee and ankle jerks were livelier on the right side than on the left.

The liver diminished in size as the illness progressed. Ascites and generalized edema developed and coma set in despite intensive intravenous glucose therapy.

The necropsy demonstrated the presence of subacute liver atrophy and subacute pancreatitis.

Case 5. A male, aged 31 years, had suffered an attack of lumbago four years previously. Recently excruciating pain developed in the posterior aspect of his right

thigh and leg. The Lasègue and Patrick signs were positive. The condition was diagnosed as acute sciatic neuritis.

The icterus index of the blood was 15 and the bilirubin content 0.6 mg. per 100 c.c. (slightly elevated above normal). Ten days later these figures were still elevated. After a fortnight, the icterus index and the bilirubin content of the blood decreased to 8 and to 0.3 mg. per 100 c.c. respectively (normal values). The blood cholesterol was 250 and later 235 mg. per 100 c.c. The ester partition was normal. The urobilin content of a 24 hour specimen of urine was normal. Tyrosine [8] was not demonstrable in the urine. The galactose tolerance test showed a normal result. The cinchophen oxidation test [9] indicated moderate liver cell function impairment. On successive tests, 33.5, 33.0, 31.0 and finally 13.5 per cent of the test dose of 0.45 gram of cinchophen were excreted as oxy-cinchophen. Normal subjects excrete less than 21 per cent of this partial oxidation product in the urine after the test dose. The decrease in the latent jaundice, and in the oxy-cinchophen excretion occurred simultaneously with the subsidence of the pain. The patient was observed over a period of six weeks.

Comment

Liver function has rarely been studied in patients with sciatic neuritis. The levulose tolerance test was applied by Miller [6] to 18 cases of sciatica with evidence of diminished tolerance in five. Eppinger noted liver function disturbance in five cases of polyneuritis and implicated a hepatic factor even in subjects with definite histories of lead and alcohol poisoning. I observed a marked spontaneous phenoluria or cresoluria in the urine of a female subject suffering from severe sciatic neuritis some years ago while studying tyrosinuria by means of the tyrosinase reaction. (The phenols and polyphenols give a pink reaction with this ferment, while tyrosine produces melanin, a brownish black, or violaceous pigment, specifically.) In the subject with sciatic neuritis reported above (case 5) the icterus index and the quantitative Van den Bergh reaction demonstrated a latent icterus. This subsided with the pain as did the liver function impairment recorded by the cinchophen oxidation test of liver cell function. Thus there is evidence that sciatic neuritis may be accompanied by subclinical hepatic damage.

An analgesic effect attributed to the jaundice was noted in some instances. The relief from pain was greater than could be expected from confinement to bed alone. The pain was noted to recur in one instance as recovery from liver injury took place (case 3). The possible analgesic influence of retained bile salts in jaundice was considered [5] and the analgesic properties of bile salts were therefore tested experimentally. When introduced into the spinal canal of cats, an analgesic effect was not noted.[10] It is suggested that associated disturbances in mineral and water metabolism observed in acute liver degeneration may possibly contribute to the analgesia since some synthetic analgesics also alter water and electrolyte relationships of cells.

Careful interrogation has eliminated the possibility of cinchophen in any form in three of the cases of sciatica complicated by jaundice. In case 4 a single dose of cinchophen (5 grains) had been injected intravenously. In case 3 the patient, a physician, had taken novatophan, 18 years previously, for an attack of sciatica. For his recent recurrent sciatic pain this drug

was not used. In case 1 the only medication taken over a period of six months was ten grains of acetylsalicylic acid, despite excruciating sciatic pain. I doubt whether the ingestion of a single or a few doses of cinchophen in these two cases played any rôle in the causation of jaundice. The administration of single doses of this drug to patients with frank liver damage appears to have no ill effect.[9] The possibility that liver injury may result from an idiosyncrasy to this drug in certain individuals with or without latent liver insufficiency cannot however be dismissed, but is unlikely in these two instances.

In the cases reported there was no history of alcohol abuse, or lead poisoning to account for the sciatic neuritis. No other nerves were involved. There was no clinical ground for suspecting a vitamin B_1 deficiency.

Summary

Five cases are reported in which the symptoms of sciatic neuritis preceded the onset of clinical evidence of liver damage and jaundice. In three instances the jaundice and liver disease occurred in persons who had not ingested cinchophen in any form.

These observations suggest that endogenous toxic substances, responsible for the peripheral neuritis involving the sciatic nerve, may also be responsible for liver injury.

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THE RESPONSE TO THE FEEDING OF CEVITAMIC ACID IN NORMAL AND DEFICIENT SUBJECTS AS MEASURED BY A VITAMIN C EXCRETORY TEST *

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THE criterion for the diagnosis of scurvy had been, until recently, the appearance of the symptoms of scurvy. As a result of the experimental work in vitamin C, three new diagnostic procedures have now come into use: the capillary resistance test, the concentration of vitamin C in the blood and the urinary excretion of vitamin C.[1, 2, 3, 4, 5] There is still some controversy as to the value of capillary resistance tests as an index of vitamin C deficiency. We have studied the capillary resistance of 25 young normal adults by the Dalldorf method [5] and found no definite relation between vitamin C excretion, capillary resistance and diet. In this respect our findings agree with those of Anderson, Hawley and Stephens.[6] It is our impression that capillary resistance is influenced by several factors and although it is usually low in patients with scurvy, it is not as reliable an index of the degree of vitamin C deficiency as is the excretion of vitamin C or the blood vitamin C.

In this study the vitamin C excretory test, described in a preliminary report,[7] was used not only to verify the diagnosis of scurvy and vitamin C subnutrition, but to study the response of such subjects to vitamin C therapy.

Procedure: Three groups were studied: a normal group of 12 young adults whose diet was adequate in vitamin C; a group of 3 normal subjects with no evidence of scurvy but whose diets were low in vitamin C and a third group of 22 patients with clinical evidence of scurvy.

The three hour excretion of vitamin C following the intravenous test dose of 100 mg. of cevitamic acid was determined in all three groups. In the normal and subnutrition groups the excretion of vitamin C was also determined for the total 24 hours. Following this, vitamin C as cevitamic acid (Merck & Co.) was fed to nine of the normal subjects, to the three subnutrition subjects and to all of the patients with scurvy.

In addition, to ascertain whether there was an advantage in using a larger test dose than the one originally advised (100 mg. of cevitamic acid), a group of normal and of scorbutic subjects were given an intravenous injection of 100 mg. of cevitamic acid and after an interval of two days an injection of 500 mg.

1. *In the Normal Subjects and in the Subjects on Diets Low in Vitamin C.* During the experimental period the subjects remained on their regular

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diets, being careful to avoid any change in the intake of food high in the vitamin. The urines were collected as follows: The subject voided one to one and a half hours after breakfast. This specimen was discarded. The urine was then collected for the next three hour period and the vitamin C excretion determined. The urine was also collected for the following 21 hours. The next day, after voiding, the subject was given intravenously 100 mg. of cevitamic acid (Merck & Co.) and the urines were collected in the same way as before. Vitamin C feeding was then begun as cevitamic acid 50 to 100 mg. daily and the tests were repeated at intervals.

2. *In patients with scurvy* the same procedure was followed as in the normal subjects, with this difference that in the severe cases the cevitamic acid was at first given intravenously and then in larger daily doses. When given by mouth, the cevitamic acid was fed at 12 noon and 4 p.m. Cases 22 and 28 had received some orange juice prior to our original excretory determinations.

3. *Comparison of the 100 mg. and 500 mg. Test Doses on the per cent of the Vitamin Excreted in Three Hours.* In ten normal subjects intravenous test doses of both 100 and 500 mg. of cevitamic acid were given. An interval of two days elapsed between these two test doses; the 100 mg. dose was given first. The urines were collected in the usual manner. This procedure was also carried out on eight patients with scurvy. In this study the urines were not collected for the 21 hours following the three hour test period.

4. *Method of Estimating Vitamin C in Urine and Blood.* Vitamin C was determined by titration against a standardized solution of 2:6 dichlorophenolindophenol by the method of Birch, Harris, and Ray.[8] All necessary precautions were taken to insure against loss of the vitamin. The urines were acidified to 10 per cent of their volumes with glacial acetic acid. The three hour specimens were titrated immediately. Of the 21 hour specimens, those voided before supper were done immediately and the remaining specimens were collected in dark bottles in which there was a given amount of acetic acid and these were kept in the ice box. We have, as many other observers, studied the rate of destruction of the vitamin in urine and found that in acidified urine, kept in the cold, there is very little loss within 12 to 16 hours.[9] It is also important that the urine in the bladder should be acid, especially in patients with a low excretion of the vitamin.[10] Where there was a tendency for the subject to excrete an alkaline urine, small doses of ammonium chloride were given. This was necessary in four cases.

Blood vitamin C was determined on 15 of the scurvy patients and on nine of the normals by the Farmer and Abt method.[4]

Results

1. *Normals.* Table 1 gives the age, weight, height and capillary resistance of the normal subjects. The three hour excretion (Table 3) of vita-

TABLE I
Normal Subjects

Case No.	Age Yrs.	Weight lbs.	Height in.	Cap. Res. cm.	Diet Rating
1	23	139	66	15 cm.	3+
2	23	155	70	40 cm.	3+
3	23	165	73	15 cm.	3+
4	24	145	73	20 cm.	2+
5	23	140	69	30 cm.	2+
6	22	177	70	20 cm.	3+
7	23	170	69	15 cm.	3+
8	21	176	71	35 cm.	3+
9	22	170	71		3+
10	23	143	67	15 cm.	2+
11	25	168	70	30 cm.	2+
12	20	155	70	40 cm.	2+
13	21	170	71	20 cm.	1+
14	25	150	69	40 cm.	1+
15	21	170	72	20 cm.	2+

1+ Signifies diet low in vitamin C
2+ Signifies diet fair in vitamin C
3+ Signifies diet high in vitamin C

min C in the normal subjects on diet alone varied from 4.5 to 25 mg., the average being 12 mg. The 21 hour excretion varied from 30 to 180 mg. with an average of 67 mg. Following the intravenous injection of 100 mg. of cevitamic acid the three hour excretion rose in all the normal subjects, the total excretion varying from 24 to 81.8 mg. with an average excretion of 47 mg. The 21 hour excretion rose in four cases and fell or remained approximately the same in the rest of the group. The average 21 hour excretion was 67 mg. The intravenous test dose done after the feeding of 400 mg. of cevitamic acid to nine of this group was followed by an increased excretion within three hours in five of the nine subjects. The average excretion in three hours for these nine subjects rose to 64 mg., and in the following 21 hours rose to 88 mg., thus raising the average 24 hours excretion to 152 mg. Continued feeding of cevitamic acid in six subjects further increased the three hour excretion after the intravenous test dose. The subject in whom no further increase was effected had originally excreted 81.8 mg. of the 100 mg. injected. Three of the subjects, after continued feeding of cevitamic acid, excreted more than 100 mg. of vitamin C in the three hours after the test dose. Part of this was of course derived from the tissue stores and suggests a state of complete saturation.

2. *Subjects on Low Vitamin C Diets (Table 4).* On diet alone these subjects excreted an average of 1.9 mg. in three hours and 10.2 mg. in 21 hours, a total of 12 mg. for 24 hours. The test dose caused a rise in the three hour excretion, but this was far below that seen in the normal subjects, the average being 10.4 mg. The following 21 hour excretion was not raised but actually was lower. After feeding 1000 mg. of cevitamic acid, all three

TABLE II

Summary of Patients with Scurvy

Case No.	Sex	Age	Duration of Deficient Diet	Other Complications	Clinical Signs of Vitamin C Deficiency							Capillary Resistance Cm.	Bld. Vit. C mg. %
					Referable to the Gums					Other Clinical Signs			
					Spongy	Piled Up	Bleeding	Ulcerated	Hem. into Gums and Buccal Muc. Memb.	Massive Subcutaneous Hemorrhage	Presence of Petechiae. Location		
20	M.	40	3–4 mos.	None	+	+	+	+	Massive	Into both legs	No	30	—
21	M.	68	12 mos.	Art. scl. and hypertension	0	0	0	+	+	Both legs	Left leg	15	—
22	F.	38	3 mos.	None	0	0	+	0	+	No	No	—	—
23	F.	22	3 mos.	Malnutrition	+	+	+	0	0	No	No	20	0.35
24	M.	55	14 mos.	None	+	+	+	0	0	Both legs and popliteal spaces	No	15	—
25	M.	21	14 mos.	Possible rh. fever	0	+	0	0	+	No	No	15	—
26	F.	76	12 mos.	Art. scl.	0	0	0	0	0	No	Legs and forearms	18	0.23
27	F.	45	11 mos.	Ulcer diet	0	+	+	0	0	No	No	10	0.0
28	F.	21	12 mos.	None	0	+	+	0	0	No	No	—	1.3*
29	M.	60	3 mos.	*Strep. hem.*	0	0	0	0	0	No	Both legs	5	0.55
30	M.	71	24 mos.	Tuberculosis	0	+	0	0	0	No	Bleeding lips	—	0.0
31	M.	70	Intermittent for 3 years	None	0	+	0	+	+	No	Both legs	15	—
32	M.	56	12 mos.	Alcoholism	0	0	+	0	0	No	Epistaxis	30	0.50
33	F.	42	4 mos.	Profound malnutrition	0	0	0	0	0	No	Epistaxis	40	0.39
34	F.	52	24 mos.	Lues and arthritis	0	+	0	+	0	0	No	—	0.52
35	F.	54	Undetermined	Hyperthyroid	0	0	0	0	0	No	Both arms	—	0.19
36	M.	70	On and off for 3 years	Art. scl. and hypertension	0	0	+	+	+	No	Lower arms	20	—
37	F.	49	3–4 mos.	Fibromyoma of uterus	0	0	0	Slt.	0	No	Colored patient	—	0.65†
38	M.	44	24 mos.	Aneurysm aorta	0	+	0	0	0	No	Both arms	—	0.48
39	F.	47	Always poor	Diabetes and thrombophlebitis	0	+	0	0	0	Large purpuric spots	Arms, legs, face	30	0.35
40	M.	45	2 years	Coronary occl.	0	+	+	+	0	No	Both arms	—	0.37
41	F.	45	5 years	None	+	+	0	Slt.	0	No	No	—	0.59

* Patient had been on orange juice daily for 6 days prior to this determination. † Blood taken 2 hours after breakfast.

TABLE III

Mg. Vitamin C Excreted in Normals Following Injection of 100 Mg. Intravenously, before and after Feeding Cevitamic Acid

Case No.	Mg. Excreted on Diet		Mg. Excreted after Test Dose of 100 mg. I.V.		Mg. Excreted after 400 mg. and Test Dose		Mg. Excreted after 850 mg. and Test Dose		Mg. Excreted after 1800 mg. and Test Dose		Mg. Excreted after 2050 mg. and Test Dose		Mg. Excreted after 3000 mg. and Test Dose	
	Hours		Hours		Hours		Hours		Hours		Hours		Hours	
	3	21	3	21	3	21	3	21	3	21	3	21	3	21
1	25.4	180.7	52.7	125.8	51.2	93.3	62.3	132			58.5	107	72	154
2	9.0	53.2	24.2	87.1	60.0	108.9			147.0	91.8				
3	16.8	81.6	81.8	73.8	107.7	76.1			86.0	184				
4	21.2	44.7	67.0	89.3	46.5	124.9			103.7	71				
5	8.5	109.0	40.5	104.0	38.7	137.3	41.8	128.3			113.0	87		
6	6.4	31.1	32.0	34.6	54.1	82.0	38.6	49.9			74.0	77		
7	10.9	36.1	57.8	65.7	56.7	41.0								
8	12.9	30.1	44.6	49.3	94.0	89.3								
9	4.9	39.7	43.5	25.1	73.9	40.1								
10	4.5	58.9	47.8	53.5										
11	12.1	51.9	37.6	47.9										
12	10.9	86.9	34.4	80.9										

TABLE IV

Mg. Vitamin C Excreted in Normals on Diet Low in the Vitamin, after a Test Dose both before and after Feeding Cevitamic Acid

Case No.	Mg. Excreted on Diet		Mg. Excreted after Test Dose		Mg. Excreted on Test Dose after Feeding 1000 mg.		Mg. Excreted on Test Dose after 1500 mg.		Mg. Excreted on Test Dose after 2000 mg.	
	Hours		Hours		Hours		Hours		Hours	
	3	21	3	21	3	21	3	21	3	21
13	1.4	9.5	11.5	4.8	52.8	39			57.9	60.8
14	2.2	11.7	5.6	1.6	44.1	39	67.2	65.9		
15	2.3	9.5	14.2	9.1	36.2	20.6			53.3	22.5
14*			2.7		17.1†		38.5			

* Second study after an interval of 3 months.
† Amount of cevitamic acid fed at the time of this test was 650 mg.

subjects excreted more than 36 mg. of the injected vitamin, the average being 44 mg. The 21 hour excretion rose, but was not as high as the average excretion in the normals on diet alone. Continued feeding of cevitamic acid caused an increase in the three hour excretion following the test dose and the 21 hour excretion rose in two of the subjects. Case 14 was studied a second time after an interval of three months, during which time he had received no cevitamic acid. The excretory test was again low, 2.8

mg. After feeding 650 mg. of cevitamic acid, the excretion after the test dose rose to 17 mg. and after feeding 1500 mg., 38.5 mg. were excreted.

3. *Patients with Scurvy.* (A) *Symptoms:* Table 2 summarizes the symptoms and signs of vitamin C deficiency observed in the 22 cases studied Only six cases were uncomplicated. Malnutrition was profound in two cases. Arteriosclerosis in varying degrees was present in four cases. Symptoms referable to the gums were found in 16 cases. These varied considerably, but definite piling up of the gums with retraction from the teeth was present in 13 cases. Hemorrhage or petechiae or both were found in 15 patients. The capillary resistance done in 13 cases was low in nine. The blood vitamin C, done in 15 cases, was below 0.55 mg. in twelve. In one case, number 28, the patient had had orange juice for one week before the study and the blood vitamin C was normal.

(B) *Excretion in Patients with Scurvy (Table 5).* These patients were on the wards of the Third (New York University) Medical Division, Bellevue Hospital. Cases 22, 28 and 41 were studied in the Metabolism Clinic of the College of Medicine Clinic, New York University. Case 26 was studied twice, once in the clinic and later in the hospital. Prior to the administration of vitamin C, the average three hour excretion in the scurvy patients was 1.4 mg. In some cases no vitamin C was titratable in the urine; in four cases it was less than 1 mg. The 21 hour excretion averaged 6 mg. After the 100 mg. test dose of cevitamic acid, the average three hour excretion was 2.5 mg. The 21 hour rose to an average of 10 mg. In cases 20, 21, 29, 30, 31, 39 and 41 cevitamic acid was given intravenously until clinical improvement was noted and then by mouth. The tests were repeated at frequent intervals after the feeding of the vitamin and in six cases (23, 26, 27, 31, 32, and 36), the excretion was followed daily during the patient's stay in the hospital. The other patients were followed at weekly or semiweekly intervals. In five cases (33, 34, 35, 37 and 38) although cevitamic acid was administered, excretory tests were done only after the test dose. In table 5 the excretory tests following the administration of cevitamic acid are reported. As it would require too much space to report every case in detail, this table summarizes the results at intervals during the studies. In those cases where the excretion was determined daily, it was found that the excretion remained low for from 4 to 12 days and then approached the normal. The amount of cevitamic acid required to bring the excretion to the normal level depended on the duration of the deficient diet and the presence of complicating conditions.

4. *Comparison of 100 mg. and 500 mg. in Test Doses of Cevitamic Acid on the Three Hour Excretory Test.* Ten of the normal subjects (1, 3, 4, 5, 6, 7, 8, 10, 12, 13 and 15) were given intravenous test doses of 100 mg. of cevitamic acid and two days later 500 mg. These tests were carried out three months after the original studies were completed. The normals excreted an average of 53.8 per cent in three hours after the 100 mg. test dose and 55.8 per cent after the 500 mg. test dose. Undoubtedly the higher

excretion within three hours represents a higher dietary intake of vitamin C. These normal subjects had become vitamin C conscious as a result of these studies and almost all had increased their daily intake. Eight patients with clinical signs of scurvy were similarly tested. The average three hour excretion after the 100 mg. dose was 1.6 per cent, after 500 mg., 7 per cent.

The results on the normal subjects show that there is no particular advantage in using the larger test dose of cevitamic acid. In the patients with scurvy, apparently the per cent excretion is somewhat higher following the larger dose. If such a dose were to be used, it would merely require establishing the limits of the three hour excretion. We feel, however, that as

TABLE V

Vitamin C Excretion in Patients with Scurvy as Measured by Test Dose before and after Feeding Cevitamic Acid

Case No.	Mg. Vitamin C Excreted on Admission		Mg. Vitamin C Excreted after Test Dose before Feeding Cevitamic Acid		Effect of Feeding Cevitamic Acid on 3 hr. Excretion Following Test Dose		Remarks
	3 hr.	21 hr.	3 hr.	21 hr.	Mg. Fed	Mg. Excreted	
20	3.3		3.6		1400 4550 6100	15.5 57 86	Given intravenously up to 3600 mg.
21	2.2		1.3	4.7	800 2200 4000	1.4 3.3 8.0	Given intravenously up to 3300 mg.
22	not	done	7.9*		2500	34	*Had taken orange juice for 1 week before tests. Cevitamic acid given orally
23	2.1	8.2	3.9	12.9	2700	95	Cevitamic acid given orally
24	0		0		2000	0	Cevitamic acid given orally—never excreted any in urine but symptoms cleared
25	2.0	6.2	Tr.	0			Left hospital
26–1	0.4	3.0	0.5		1100 2600	16.5 33.2	First study done in clinic Cevitamic acid always given orally
26–2	0.7	1.5	0.3		2600	32.0	2nd study after interval of 6 weeks with no cevitamic acid
27	0.3	0	1.0	0	2000 6660	28.3 59.2	Cevitamic acid given orally
28	0.2		9.7	23.9	900 1700	19.0 70.8	Clinic pt. had taken orange juice for 1 week before tests Cevitamic acid given orally

TABLE V—*Continued*

Case No.	Mg. Vitamin C Excreted on Admission		Mg. Vitamin C Excreted after Test Dose before Feeding Cevitamic Acid		Effect of Feeding Cevitamic Acid on 3 hr. Excretion Following Test Dose		Remarks
	3 hr.	21 hr.	3 hr.	21 hr.	Mg. Fed	Mg. Excreted	
29	2.0		4.7	14.1	400 800	3.3 1.7	Cevitamic acid 500 mg. intravenously
30		0.8	1.8	21.5	1200	5.9	Cevitamic acid given intravenously
31		0	0.4	1.5	1500 4200 6700	0.9 45 55	3300 mg. cevitamic acid given intravenously, after this, orally
32	0.7	5.2	2.3	6.6	1500 3400 5900	15 45 48	Cevitamic acid all given orally
36	0.7	2.0	0.5	1.83	1500	0.3	Cevitamic acid given orally
39			1.4		1200 3100 4600 5600 6700	2.9 3.5 7.7 14 30	1500 mg. of total amount of cevitamic acid were given intravenously Pt. a diabetic
40			1.6		1500 2300 4000 6700	3.9 3.3 3.7 25.0	Pt. had coronary occlusion Cevitamic acid by mouth
41			2.4	8.1	4600 8600	32.0 50.0	600 mg. intravenously, then orally

the smaller test dose gives consistent and accurate results, it is preferable to a larger one because in following the excretory response to vitamin C therapy, there is less chance of saturating the patient when the smaller dose is used.

DISCUSSION

From these studies it is obvious that normal young adults on a presumably normal diet will excrete varying amounts of vitamin C daily. The question arises as to what constitutes a normal excretion. From our results and the results of other investigators [1, 2, 3] there is apparently a rather wide range of excretion in the normal which is naturally influenced by diet. In view of the difficulties of collecting 24 hour urine specimens and of protecting against loss of the vitamin in urines collected over a long period of time, we have attempted to evaluate the significance of the excretion for a three hour period after an intravenous test dose of cevitamic acid. The three hour ex-

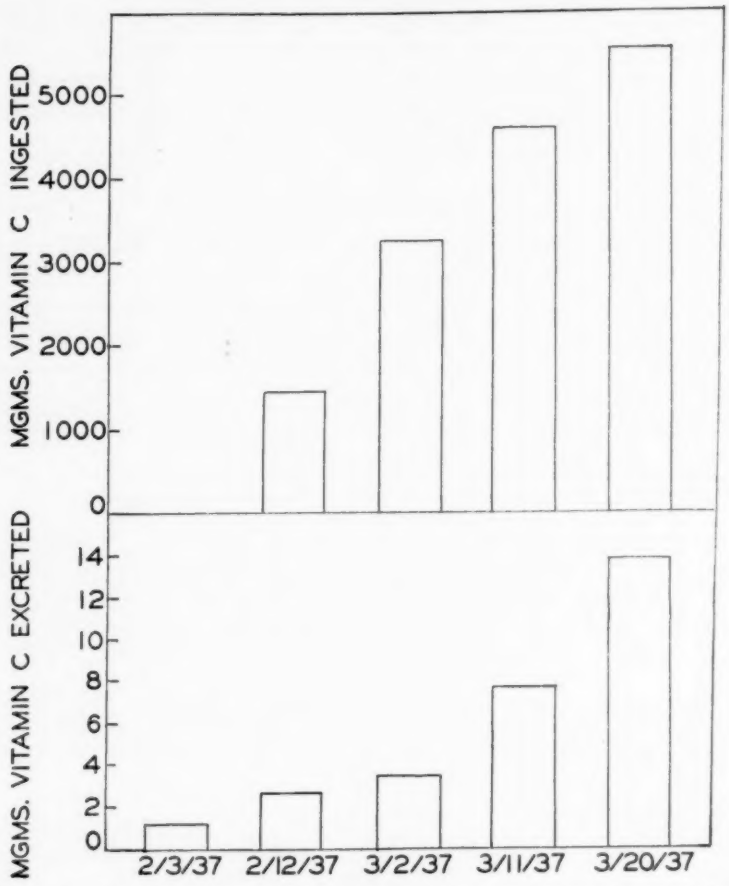

FIG. 1. *Case 39.* The three hour excretion tests before and after the administration of cevitamic acid.

cretion on diet alone may be fairly low in normal individuals. If, however, one studies the three hour excretion following an intravenous test dose of 100 mg. of cevitamic acid, the difference in excretion between normal subjects, scorbutic subjects and subjects on a low vitamin C diet is quite definite. Of the 12 normal subjects studied prior to feeding any additional vitamin C, 11 excreted more than 32 per cent of the injected vitamin in three hours. Of the three subnutrition subjects all excreted less than 15 per cent in three hours and in the subjects with scurvy, excluding cases 22 and 28 who had been receiving orange juice prior to the original test, all excreted less than 5 per cent in three hours. These results were consistent with the 24 hour excretion. It seems reasonable, therefore, to suggest that the excretion of vitamin C following an intravenous test dose of 100 mg. can serve as an index of whether or not the subject is deficient in vitamin C.

The results of feeding vitamin C to these three groups of patients bring out the fact that the normal subjects excreting less than 80 per cent of the

injected vitamin in three hours can be stimulated to excrete larger amounts following the feeding of vitamin C. One may infer that when more than 70 per cent of the injected vitamin is excreted in three hours, the tissues of the individual are well saturated with the vitamin. This does not mean, however, that complete saturation of the tissues is necessary in an individual in order to have a normal state of vitamin C nutrition.

The subjects on the low vitamin C diets responded very promptly to the feeding of vitamin C and their three hour excretion reached the normal level after the feeding of 1000 mg. of cevitamic acid. In this respect they show again the difference between subnutrition and absolute deficiency of vitamin C. The scorbutic patients required much larger doses before their three hour excretion test fell within a normal range. In fact in some instances this did not occur during the period of these observations.

The diets of the subnutrition cases are the ones of most interest in the field of nutrition. The three subjects studied were medical students and their diets were low in fresh fruit and in uncooked vegetables. Practically none of these men took any oranges and only occasionally an apple. Their response to the feeding of cevitamic acid suggests that their tissue reserves of the vitamin were low, but apparently had not reached the stage where any demonstrable clinical or pathological effect could be found. The capillary resistance in two of these subjects was 20 cm. and was 40 cm. in the third subject. It is quite likely that pathological changes in the tissues as a result of vitamin C deficiency do not occur until an absolute state of deficiency has existed for some time. Youmans and his associates [11] found that of 15 subjects whose diets were inadequate in vitamin C, 12 excreted less than 20 mg. of the vitamin in the urine daily. The 24 hour excretions in our subnutrition group substantiate these findings.

Of the 22 cases showing symptoms of scurvy, only six cases were uncomplicated by other diseases. This brings up the fact that vitamin C deficiency is probably seldom uncomplicated and that other pathological states may increase the vitamin C requirement of the individual. Administration of cevitamic acid improved the clinical symptoms in all cases; in several cases this improvement was apparent before the excretory test had reached the normal level.

Summary

1. The three hour urinary excretion of vitamin C before and after an intravenous test dose of 100 mg. of cevitamic acid was studied in a group of 12 normal adults, 3 normal individuals on diets low in vitamin C and 22 cases of scurvy.

2. The three and 21 hour excretion was studied in the same group after an intravenous test dose of 100 mg. of cevitamic acid and the intravenous test dose was repeated in all three groups following the feeding of cevitamic acid.

3. Following the intravenous test dose the 12 normal subjects excreted an average of more than 40 per cent of the injected vitamin within three hours. The extremes were 24 to 82 mg. The three subnutrition cases excreted 5 to 14 mg. The cases with scurvy excreted from 0 to 5 mg.

4. Following the feeding of 1000 mg. of cevitamic acid to the subnutrition subjects, the three hour excretion rose to the normal level after the test dose. In order to increase the urinary excretion to the normal level in the patients with scurvy much larger amounts of the vitamin had to be fed. In the normal group the feeding of cevitamic acid in small doses increased the vitamin C excretion above the original level.

5. Excretion tests were also done following an intravenous test dose of 500 mg. of cevitamic acid in normal and scorbutic subjects. The normals excreted an average of 55.8 per cent; the scorbutic patients an average of 7 per cent of the injected vitamin.

6. As a result of these observations it is suggested that the urinary excretion of vitamin C following an intravenous test dose of 100 mg. of cevitamic acid will serve as an index of vitamin C deficiency or subnutrition and as a guide to show the degree of saturation of the tissues following the feeding of cevitamic acid.

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PEPTIC ULCER: THE EFFECT OF THE ADMINISTRATION OF BILE ON THE BEHAVIOR OF THE DISEASE *

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Two reasons prompted us to administer bile to patients with peptic ulcer: the evidence from experiments with animals that ulceration of the stomach or duodenum may follow the diversion of bile from the duodenum, and certain other evidence which suggests that the disease may result from some type of deficiency.

Numerous studies have been reported in which ulceration has developed after interference with the normal secretions in the duodenum. A review of the literature on this subject has been published by us in two previous articles [1, 2] and will not be repeated here. Briefly, the various experimental methods that have been most successful in producing peptic ulcerations in animals, usually dogs, have involved side-tracking or shutting off the flow of bile or pancreatic juice to the duodenum, or damaging the liver, as by chemical poisons, cinchophen, etc. These studies may be divided into three groups:

(1) Experiments which have severed the duodenum from the stomach, and in this way prevented a normal mixing of hydrochloric acid with the duodenal secretions, succus entericus, bile and pancreatic juice.

(2) Experiments which have diverted only one of these three secretions.

(3) Experiments which have caused damage to the liver.

In addition, there have been observations, both in animals and in man, of spontaneous ulceration in association with a diseased liver.

The experimental work included under groups 1 and 2 was inspired by the conception that ulcer might be the result of a defect in the process of neutralization of the gastric juice by regurgitated alkaline duodenal contents. The results of this work support the contention that unneutralized hydrochloric acid can damage the mucous membrane. However, it is difficult to apply the interpretation of these results to an explanation of the cause of ulcer in man. One cannot consider the damaging effect of the acid without considering the resistance of the mucous membrane to that effect. Indeed, most investigators have felt that trauma and the resistance of the mucous membrane are important factors in determining whether these experimental ulcers develop. As these complex experiments were carried on, it was found that tying off either the biliary or pancreatic ducts might be followed by the development of an ulcer. A question then naturally arose as to which was

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the more important of the two. On this question various observers have disagreed. Ivy and Fauley,[3] Elman and Hartman [4] have found a high incidence of ulcer formation in animals following interference with the normal flow of pancreatic juice into the duodenum. Conversely, Kapsinow,[5] Weiss and Hubster,[6] Berg and Jobling,[7] Bollman and Mann,[8] and others have found a higher percentage of ulcer formation following interference with the normal flow of bile. Berg and Zucker,[9] and Berg [10] comparing the frequency with which ulcers followed the diversion of bile or pancreatic juice found the greater incidence of ulcer formation after the exclusion of bile.

The evidence at present suggests that the loss of bile is the more important of the two. Strengthening this idea is the recent work reported by Blanck [11] in which ulcers developed in five of eight dogs after the complete external drainage of bile. Moreover, he claims to have prevented the development of ulcerous lesions in three other dogs similarly treated by refeeding the bile drained off. It is unfortunate that after the lesions developed, he did not attempt to bring about their healing by the administration of bile. It is evident that the lack of either bile or pancreatic juice in the duodenum, or the loss of these substances will frequently result in the formation of an ulcer in experimental animals. But, the explanation that these lesions are the result of an inadequate neutralization of the gastric juice seems to rest on insecure evidence. Certainly, this explanation cannot easily be applied to the behavior of ulcer in man.

Our present knowledge about peptic ulcer logically divides our theories on its etiology into two groups: (1) that peptic ulcer is due to the destructive effect of hydrochloric acid on a normal mucous membrane, or (2) that the disease results from a local decreased resistance of the tissues to peptic activity of the gastric juice. There is undoubted evidence, both experimental and clinical, that peptic activity plays a rôle in the development of ulcerous lesions (Mann and Williamson,[12] Matthews and Dragstedt,[13] Lindau,[14] and others). However, there is no evidence that it is the sole cause of the lesion. If the ulcer is associated with the hydrochloric acid, changes in the activity of the ulcer must be associated with a change either in the acid, or in the resistance of the tissues to the damaging or corrosive effect of that acid. There is no evidence that the quality of the human gastric juice varies with a change in the state of the ulcer which would seem inevitable if the destructive effect of the juice were the important factor in the development of the lesion. Recently, Schnitker and Evans [15] have reported that there is no change in the quality or quantity of human gastric juice from the period of a preulcerous state to the time when an active lesion could be demonstrated. Moreover, there are a sufficient number of cases of ulcer with low acid values to make it seem probable that peptic ulcer in man depends upon something other than, or in addition to, the destructive effect of the hydrochloric acid. The progressive susceptibility of the lower intestine to the corrosive effect of the gastric juice suggests the importance of

the normal resistance of the tissues to this damaging influence. Also, it is difficult to believe that the factor of safety in the mechanism for neutralization of the hydrochloric acid is so slight that a diversion of either one of the alkaline juices is sufficient to leave the duodenal mucous membrane unprotected.

The other theories, such as the neurogenic, vascular, and infectious fall into the second group, implying a decreased tissue resistance. These theories are based more upon clinical observation than upon experimental work. The experimental ulcers which most resemble those found in man have been produced only by technics similar to or related to the Mann-Williamson operation. This does not lend support to the neurogenic, vascular, or infectious theories.

That a deficiency of some kind may be the cause of ulcer is a possibility which has received little attention, although there is much in the behavior of the disease to make tenable such an hypothesis. The clinical behavior of the disease is comparable in many ways to that of pernicious anemia, which is also chronic, passing through alternating cycles of activity and quiescence, and being influenced by emotion, fatigue, and infection, similarly to ulcer. All the experimental work based on the operative principle stressed by Mann and Williamson, of necessity interferes with the normal physiology of the gastrointestinal tract. There has not been excluded the possibility that the formation of ulcer may depend upon a disturbance in digestion which results in a deficiency. The fact that a diversion of any of the secretions found in the duodenum will produce an ulcer, favors the idea that a disturbance in digestion is the cause of the disorder as much as, if not more, than it favors the theory of failure in neutralization of the gastric juice as a causative factor. Supporting this idea of "deficiency" are the studies carried out by McClure and Huntsinger [16] in which they found that in 8 of 12 patients with symptoms of an uncomplicated duodenal ulcer, the biliary fraction was "decidedly abnormal," particularly with respect to the bile acids.

In summary, therefore, we have been led to administer bile to patients with peptic ulcer because of the reports in the literature of instances in which lesions of the gastric or duodenal mucosa have been associated both in animals and in man with interferences with the normal flow of bile into the duodenum; because the absence of bile seems to be more important than loss of pancreatic juice in the formation of ulcer; because peptic ulcer may be considered a type of "deficiency" disorder in which a loss of the protective mechanism of the duodenal mucosa allows ulcers to develop; and, because studies of the bile have shown an abnormality in cases of duodenal ulcer.

The administration of bile to patients with gastric complaints, or even peptic ulcer, is not new, although at the present time there is much more experimental and clinical data to suggest and warrant its use than was available to the previous experimenters. About 1913, Palfrey [17] in this country, and Glaessner [18] in Germany discussed the treatment of peptic

ulcer with the use of bile. Both writers reported symptomatic improvement in their cases. Jarno [19] in 1926 and Thom [20] in 1932 have also discussed the effect on patients of a preparation called "salvacid." According to Thom this preparation contains fel tauri sicca, Thujoncholylglyzin, acetyloglycocholic acid, together with calcium carbonate and sodium bicarbonate.

Observations

Based on these considerations we began the administration of desiccated ox bile to patients with peptic ulcer in January 1934 and continued its use over a period of two years. We wished to use a product of bile which would be convenient to give and at the same time would be as similar to fresh bile as possible. Because the moderately high temperature to which the usual preparations of bile are subjected might change the quality of its ingredients, we asked the Burroughs and Wellcome Company for suggestions to overcome this difficulty. After some study their laboratory found that by mixing the bile with exhausted licorice root one could dry the preparation at a temperature below 38 degrees centigrade. They gave us enough of this material to carry out the study reported herein. We should like to take this opportunity to express our appreciation of the cooperation and many courtesies extended by the various members of the company.

The bile was enclosed in gelatin capsules containing 0.3 gram, 0.5 gram, and 0.75 gram. The larger capsules proved unsatisfactory because some of the patients found them difficult to swallow. Ultimately, we used only the 0.3 gram capsules.

It was difficult to know how much bile should be given in treating these patients. As previously stated, if peptic ulcer depends upon a disturbance in the biliary secretions, this disturbance may be in the nature of a quantitative or of a qualitative abnormality. Except for the work of McClure and Huntsinger, which suggests that a qualitative difference occurs in the bile of patients with ulcer, there is little information on the subject. We had no other choice than to give as much as a patient could tolerate. Before beginning the treatment of patients with ulcer, we determined the amount of bile that could be tolerated by individuals with no gastrointestinal disease. Eighteen such patients who were on the medical wards of the Peter Bent Brigham Hospital were given increasing amounts of bile. It was found that individual patients varied in the amount which they could tolerate. On the average these persons could take 3.0 grams of our material a day if given in divided doses. A few were able to tolerate 4.0 grams but some were upset by 2.5 grams. The ill-effects consisted of anorexia, nausea and slight diarrhea. Occasionally a patient complained of slight epigastric burning. We utilized these data to establish an upper limit of dosage of 3.0 grams per day in our patients with ulcer, and attempted whenever possible to give this maximum amount. Nearly all the patients were able to take

daily a dosage of two capsules of 0.3 gram of bile every two hours for five doses.

Altogether we have treated 40 patients with peptic ulcer. As established by the roentgen-ray, four had gastric ulcers, 32 had duodenal ulcers, and four had both. All the patients were seen and followed in the gastro-intestinal clinic of the out-door department of this hospital, and except for one or two instances, they were ambulatory throughout the course of treatment. The duration of symptoms varied from 1 month to 25 years, with an average of 5.7 years. Ten of the group had received no previous treatment, whereas the others had been given various types of ulcer therapy. We endeavored to limit the treatment to therapy with bile only, but this was not always possible. Based on this fact, the 40 cases have been divided into two groups: (1) those whose therapy consisted of bile only, and (2) those who received some alkaline treatment in addition to the bile. Both groups were given a normal diet. It seemed wise to give these patients some kind of menu in order to guard against foolish excesses. Having used this diet for many years, we know that it will not of itself control the symptoms of ulcer.

A few patients complained of epigastric burning shortly after the ingestion of a capsule. We found this could be eliminated by the use of a full glass of water at the time the capsules were taken.

Group 1—Patients Treated with Bile Alone. There were 23 patients who were treated with bile alone. These individuals had had symptoms of ulcer from 1 to 22 years, with an average of 4.5 years. The duration of treatment varied from one week to two years (average 6.18 mos.), depending upon the results and the degree of coöperation obtained. The treatment in all instances was continuous. None of the patients was treated longer than two years. The results have been classified into four groups: The first consists of seven patients who had "excellent" results. (Followed for an average of 7½ mos.) These individuals were promptly relieved of all symptoms and continued to be free from complaints throughout the course of their treatment with bile. The second group comprises seven cases that had "good" results, with definite amelioration of their discomfort; they did have, from time to time, mild symptoms that could be recognized as coming from the ulcer. (This group was followed for an average of 7¾ mos.) In the third group were three patients who had "fair" results, that is, they had less trouble than before the treatment was begun, but the results were not satisfactory from the point of view of either the patient or ourselves. (These were followed for an average of 6½ mos.) In the fourth group were six patients who are classified as "failures" in that they did not receive any benefit whatever. Some of these refused to follow the treatment long enough for us to judge whether they would have received any improvement if the treatment had been continued longer. (These were followed for an average of 2¾ mos.)

As in all chronic diseases, the evaluation of the effect of therapy is very difficult in peptic ulcer. Our results would imply that bile is not a specific cure for the disease. However, as we followed these cases, the results were so striking in certain individuals that they seemed worthy of a careful analysis. The first thought which occurred to us was that the difference in results might be due to psychotherapy, a most important factor in the institution of any new form of treatment. We tried to avoid enthusiastic suggestions as much as possible. In addition, we attempted to classify these patients according to temperaments, without finding any striking differences in the groups. We could not convince ourselves that the difference in results could be explained on this basis; and, if a psychic influence played a rôle, we were not able to detect it.

The factor of previous therapy for the ulcer was considered next as of possible significance. Of the seven patients who had "excellent" results, six had received no previous kind of treatment. From the seven with "good" results, three had had no previous ulcer therapy. The nine patients who had only "fair" results or had failed to receive any benefit, had all had some kind of other treatment for the ulcer. This would suggest that the opportunity to compare the effectiveness of two kinds of treatment tended to make the patients with the previous therapy less satisfied with the bile treatment. Possibly, these patients were more than normally resistant to any form of treatment.

An attempt to correlate the results with the severity of the process has not been enlightening.

The range of acidity as determined by gastric analysis in the four groups was surprisingly constant. The average for the highest acidities was as follows:

"Excellent"	Free	Acid	44°—	Total	Acid	55°
"Good"	"	"	49°—	"	"	65°
"Fair"	"	"	42°—	"	"	58°
"Failures"	"	"	53°—	"	"	67°

The incidence of night pain, which is thought by many to be an index of secretion, was the same in the four groups.

Gastric analyses were obtained before and after the therapy in nine patients of this group who had been treated with bile alone. It is of interest, although its significance is not clear, that the gastric acidity was greater in all but two of these patients after they had received bile for some time. This was true of three patients who had "excellent" results, as well as of the others.

Other comparative studies do not show any essential difference in the relative severity of the disease in patients who had poor results and in those who had satisfactory results. The duration of symptoms before the treatment with bile was essentially the same in all groups, an average of about 4.5 years. The incidence of such complicating symptoms as nausea, vomit-

ing, and bleeding, was likewise similar in the various groups. The only observation that might suggest a difference in severity was the incidence of seasonal attacks. Six of the seven patients who had "excellent" results had definite seasonal attacks of pain, and under bile therapy these patients went without symptoms through the time of year when they expected an attack. Five of the seven who had "good" results had seasonal attacks of pain and four of the five were carried through successfully with bile. In contrast to this, only two of the nine patients who had poor results with the bile treatment had a seasonal occurrence of ulcer symptoms and neither of these two was relieved. The incidence of seasonal occurrence of symptoms, then, is the most striking difference between the patients who received satisfactory results and those who did not. We are not prepared to say on what this difference rests.

Group 2—Patients Treated With Bile Together With Some Alkali. There were 17 patients who received an alkaline Sippy powder (calcium carbonate 0.6 gram, sodium bicarbonate 2.0 grams) after each meal, in other words, three powders a day, in addition to the bile capsules. Some of them also took a half glass of milk and cream once between meals, that is twice a day. It seems necessary to discuss these patients in a separate group because they were receiving more than one type of therapy and for that reason the results were more difficult to evaluate. The additional powders were given in most instances because the bile was not giving complete relief of symptoms, or because a few requested them from fear that ulcer symptoms might return. The milk was given to those few who requested it inasmuch as they liked the habit of a forenoon and afternoon drink.

This group was followed from 1 to 12 months (average 6.2 months). The length of observation was correlated to some degree with the response to therapy. On the whole these cases did not do as well as those on bile alone. However, we have classified them under the same criteria as the group treated with bile only.

(1) Two patients had "excellent" results over a period of 10.5 months observation. (2) Five patients had "good" results over an average period of eight months. (3) Six patients had "fair" results over a similar period of observation, and (4) Four patients were "failures" remaining under treatment only six to eight weeks.

Reasons for the difference in results in this group were as difficult to detect as in those who received bile alone. The duration of symptoms before treatment was as follows: "excellent"—6 years; "good"—6 years; "fair"—5.5 years; "failure"—12.5 years. The average for the group is about 7.5 years. All but one of these patients had received a previous treatment for ulcer; the one exception fell into the group of "failures." The difference in results in this instance cannot be attributed to a comparison between the effectiveness of bile and the previous type of therapy.

An attempt to estimate the emotional and nervous reactions of the patients in this group casts no light upon the difference in results. The gastric analyses showed similar findings with the exception of the " fair " group, in which the acid values were distinctly lower. The average acid values of gastric juice for these patients were as follows:

" excellent "	Free	Acid	67°	—Total	Acid	70°
" good "	"	"	64°	— "	"	111°
" fair "	"	"	29°	— "	"	45°
" failure "	"	"	66°	— "	"	82°

It is striking how similar these figures are to those in Group 1. Five patients in this group treated with bile plus small amounts of alkali had gastric analyses done before and after the treatment, without, in this instance, any essential change in the values.

Thirteen of these 17 patients had a distinct history of seasonal ulcer distress of which eight were carried through this period without symptoms. It is striking that the four patients in whom treatment failed in this group had seasonal attacks of symptoms, as opposed to the failures in Group 1 in which only two of nine cases with poor results gave a seasonal history, the other seven having continuous symptoms.

No difference could be elicited between the results on the basis of the type of symptoms from which the patient suffered. The incidence of night pain was about the same in each class and this was true also of the incidence of bleeding.

Discussion

It may be stated as almost an axiom, and certainly as an impression from observations, that *one can feed patients with ulcer disease almost anything and a certain number will respond favorably.* The literature reports good results from numerous and diverse methods of treatment. These good results may be explained by the fact, as pointed out by Emery and Monroe,[21] that a spontaneous alleviation of symptoms may extend over a long period of time in as many as 48 per cent of individuals with ulcer. Because the symptoms are easily controlled, in most instances, there is only one criterion on which to judge results. That is the prevention of a relapse. Unfortunately, we have no other method of judging the effectiveness of therapy in this disease, as we have in pernicious anemia, in which the increased number of reticulocytes is an index of the response to treatment.

From the results obtained in the treatment of these 40 patients with peptic ulcer, we must conclude that desiccated ox bile is not a specific cure for the disease. A satisfactory result occurred in only 52.5 per cent which is not much better than can occur spontaneously. This seems to rule out a disturbance in the biliary secretion as a cause of peptic ulcer in man.

However, it is our impression that the administration of bile will relieve symptoms in a definite number of patients; and this impression was

strengthened by the prevention of a seasonal recurrence in 73 per cent of the patients. The mechanism of the favorable effect is not clear. It does not seem probable that the buffering effect of only 0.3 to 0.6 gram of bile in a dose would be sufficient to explain the relief. This is supported by observations made on two cases in which aspiration of stomach contents was done shortly after the ingestion of a capsule of bile. In neither instance was there noticed an appreciable effect on the gastric acidity. Furthermore, in none of the cases, whether the responses were good or not, was there a reduction in the values of free and total acid in the gastric analyses. In fact, some of the cases with "excellent" results in Group 1 had higher values in the gastric analyses after the period of observation with bile than before, although they had suffered no symptoms. These observations forced us to conclude that the beneficial results obtained with this form of treatment were probably not due to lowering of the gastric acidity.

It is a common observation that many patients with peptic ulcer tend to have constipation. The alleviation of this symptom by the bile treatment was observed and reported spontaneously by many of the patients. Upon questioning the others who had not expressed themselves, we found that all of them had more regular bowel habits as a result of the treatment, many being relieved of a cathartic habit. Only one patient developed any symptoms comparable to those experienced by the control cases when we established the dosage of the material. Only one other individual developed diarrhea at any time, and it was promptly relieved by a slight reduction in the dose and the patient continued free of ulcer symptoms. We have found that the ability of bile to relieve symptoms is useful in those patients who have kidney disease or renal calculi in addition to an ulcer, in whom one may hesitate to push alkaline therapy. There were two patients in this series from whom renal calculi had been removed. Both patients were given only bile. They both responded very well and remained free of ulcer distress for over a year during which they have been followed.

We have pointed out previously [15] that there is no necessary correlation between the pain of ulcer disease and the roentgen-ray demonstration of a crater. This is again illustrated by three of the patients in Group 1 who were treated with bile alone. All three had responded well to the treatment. Some six to eight months after the initial roentgen-ray demonstration of a crater in the duodenum and the institution of bile therapy, repeat gastrointestinal studies were carried out. Although these three patients had been free from ulcer symptoms for these months, barium studies revealed a crater still present. Subsequent observation and studies have adequately shown that these were not instances of carcinoma.

Although bile was administered to these patients in order to learn its effect on the disease of ulcer, certain other observations were made. With the present universal interest in the study of hypertension and of means for its treatment, bile therapy too has been suggested [22] as a method of lowering the blood pressure. We observed the blood pressure in six patients with

hypertension. The ingestion of 2.0 to 3.0 grams daily of our preparation caused no changes in the blood pressure level that could not be accounted for by the normal daily variations. There was no lowering of blood pressure in a few cases without hypertension.

It has been reported [23, 24] that perhaps an excess of bilirubin in the circulation or an increased amount of bile salts in the blood, or both, accounts for the analgesic effect of jaundice on the symptoms of arthritis. Because of this observation, Sidel and Abrams have given bile salts to patients with arthritis with some gratifying results. We had under observation for ulcer, one patient who had a moderate degree of infectious arthritis, to whom we gave the bile therapy. His ulcer symptoms responded fairly well but his joint pains remained unchanged.

Summary and Conclusions

Experimental peptic ulcers in animals which appear similar to those occurring in man have followed interference with the flow of bile into the duodenum or damage to the liver. In man, ulcers have been observed associated with liver disease, and in a few instances qualitative abnormalities in the bile have been reported in cases of duodenal ulcer. These facts, plus the hypothesis that a deficiency may be the important factor in the disease of ulcer, prompted us to administer desiccated ox bile to patients with peptic ulcer.

A total of 40 patients with ulcer has been treated with bile over periods as long as two years. Four patients had gastric ulcers, 32 had duodenal lesions, and four had both. The 40 cases were divided into two groups: (1) 23 patients who were treated with bile only, and (2) 17 patients who received some alkaline treatment in addition to the bile.

The results from this treatment were as follows: Nine patients (22 per cent) had "excellent" results; 12 patients (30 per cent) had "good" results; 9 patients (22 per cent) had "fair" results, and 10 patients (25 per cent) were "failures." These figures are such as to exclude desiccated ox bile as a specific cure for the disease. However, bile may be useful as a means of relieving the symptoms of certain patients, in whom the use of alkalies is contraindicated.

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EXERCISE TESTS AND THE ELECTROCARDIOGRAPH IN THE STUDY OF ANGINA PECTORIS *

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Despite the high incidence of angina pectoris † and its varied causes, a relatively large number of patients, after most careful routine physical examination, roentgenological investigations, and routine electrocardiographic studies (including chest leads) yield findings within normal or nearly normal limits. In such cases the diagnosis must be made upon the description of symptoms obtained from the patient. According to Burnett [1] one-third of the patients, and according to the experience of Paul D. White [2] 20 to 25 per cent of the patients having angina pectoris fall within this group.

In many instances the history is so typical that a diagnosis of angina pectoris may be made with fair certainty in spite of the absence of objective findings. However, where the physician is confronted with the possibility of such a serious clinical entity, and especially where anxiety, fear, or suggestion are confusing factors, the desirability of objective evidence will be readily admitted. Such information is also important where atypical symptoms confuse the diagnosis. In addition to pitfalls in diagnosis, there are difficulties in estimating accurately the severity of this disease, the progress of the condition, and the results of therapy, all of which make objective evidence the more desirable.

In an attempt to supply this need we have been studying the effect of measured amounts of exercise on the symptoms and electrocardiograms of a number of patients. In some of the subjects the diagnosis was previously uncertain; in others a diagnosis of angina pectoris had been made unequivocally. Before describing our method and results, it will be profitable to examine the work already done in this field.

Transient changes in the electrocardiogram have been described by various investigators [3-20] during spontaneous as well as induced attacks of angina pectoris. Most of the described changes have concerned the direction of the T-waves, and the relationship of the RT or ST interval to the iso-electric line. Other subjects have shown, either alone or in conjunction with the above changes, transient bundle branch block (Bousfield [3]), transient auricular fibrillation (Parkinson and Bedford [5]; Arrilaga [12]), premature contractions (Hall [8]), lowering of the QRS voltages, and inversion of the P-waves (Vela [13]).

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† We have considered angina pectoris to be a symptom due to deficient circulation of the myocardium, rather than a disease entity in itself.

Siegel and Feil[16] have shown that such changes in the electrocardiograms do not accompany pain arising from other causes such as uterine contractions in labor or from gall-bladder or renal colic. In one patient with a gastric ulcer and paroxysmal epigastric pain, slight depression of the T-wave occurred, which varied in successive beats and was perhaps related to changes in the axis of the heart.

Whitten and Herndon[14] have carefully analyzed a series of 50 normal controls, 15 cases of angina pectoris, and a small series of patients with heart disease other than angina pectoris. This work included a study of electrocardiograms (conventional three leads) taken at rest and immediately after exercise. Eight (53 per cent) of their 15 angina pectoris patients showed some of the following changes in the electrocardiograms which were not seen in the two control groups:

"(*a*) Upright T_1 and T_2 became inverted;
(*b*) Inverted T_2 became upright. (Also in angina group that did not develop pain on test exertion);
(*c*) Iso-electric T became upright. (Also in angina group that did not develop pain on exertion);
(*d*) Upright T_2 became diphasic;
(*e*) Development of upward convexity of the RS–T interval ending in an inverted T. (Coronary T-wave);
(*f*) Increase in the "positivity" of the RS–T_3 of more than 0.1 mm. produced by exercise in an already elevated RS–T_3;
(*g*) The only Q greater than 1.0 mm. in amplitude that disappeared on exercise was in the angina group."

Many who have worked in this field have commented that in some of the normal subjects after such strenuous exertion as marathon running, there may occur a depression of RT_1 and RT_2, or RT_2 and RT_3 to as much as 1.0 mm. below the iso-electric line. This finding frequently occurs during attacks of angina pectoris. However, there is a tremendous discrepancy between the amounts of work required to produce such changes in these two groups of subjects, and furthermore, the underlying mechanism is probably the same, namely: myocardial anoxemia.

Wood and Wolferth[7] described transient changes after exercise in the RT intervals and T-waves of 15 (50 per cent) of the 30 cases of angina pectoris; Goldhammer and Scherf[17] reported similar changes in 30 (75 per cent) of 40 patients with angina pectoris; and Duchosal and Henny[6] found the test positive in 11 (58 per cent) of 19 true cases, doubtful in one, and negative in seven cases of angina pectoris. These last workers observed the test to be positive in seven of 24 doubtful cases of angina pectoris, doubtful in four, and negative in 13 cases.

It will be observed that a considerable percentage of seemingly typical cases in each of the above series showed negative electrocardiographic (3 lead) tests after exercise. Possible explanations are (1) insufficient exer-

cise in those who did not develop pain, (2) mechanisms other than anoxemia being factors, or (3) the possibility that the process was in so-called " silent areas " not reflected in the conventional three leads. It occurred to us that additional information might be obtained from a study of the effect of exercise on the chest leads as well as on the conventional three leads.

So far as we have been able to learn from a survey of the literature, Katz and Landt [18] are the only workers who have studied the effect of exercise on the chest leads as well as the conventional three leads. Personal communications [21, 22] from some of the workers in this field indicate that no work has yet been published on the effect of exercise on the chest leads of normal subjects. The series of Katz and Landt consisted of 20 ambulatory angina pectoris patients. They found transient changes in the chest leads in 11 of the 20 patients; in two of this group the changes occurred in the chest lead alone, in the other nine patients changes occurred in all four leads. That the amount of exercise (dumb-bell swinging while recumbent) may have been insufficient is suggested by the fact that pain occurred in only 13 of the 20 subjects. After reviewing their tables, we remain of the opinion that some of the changes they have described are not typical of angina pectoris. According to our own experience certain of these changes may occur in the electrocardiograms of normal subjects after exercise. We refer especially to the deepening of the normally inverted T-wave in the chest lead. Likewise, a slight depression of the RT interval may occur in any lead of some few of the normal subjects; even to 1.0 mm. ($\frac{1}{10}$ millivolt) below the iso-electric line.

We have been able to confirm the experience of most of the other workers [3-20] in this field concerning the significance of transient inversion of an upright T_1 and T_2, or an upright T_2 and T_3, and/or significant changes occurring in the ST segments, after exercise, in the electrocardiograms of subjects with known or suspected angina pectoris. We are convinced that these changes do not occur in normal subjects and that these findings must be considered positive evidence of myocardial ischemia. Moreover, our studies of the chest leads of angina pectoris patients after exercise have led us to believe that *the same significance must be given to a shift of the RT segment in the negative direction or the temporary disappearance of the Q-wave in this lead, or a change from a normally positive T-wave to a negative one.* These changes have never been seen in our normal subjects. In the series of Katz and Landt,[18] the upward (negative) shift of the RT in the chest lead occurred four times in 20 tests: three times with changes in the conventional leads and once alone. Whitten and Herndon [14] found one patient among 15 with angina pectoris in whom a Q-wave in the conventional leads greater than 1.0 mm. in amplitude disappeared after exercise.

We are collaborating with Drs. Grant Otis and Joseph K. Bradford in a study of the effect of exercise on the chest lead as well as on the conventional leads of a group of normal subjects. This work will form the basis of another publication.

So far we have studied the effect of exercise on the conventional as well as Lead V of a group of 40 normal individuals varying in ages from 20 to 55. After such exertion as rapidly ascending from three to six flights of stairs, we have noted in addition to the temporary increase in rate the following transient changes in the electrocardiograms: In some, the T-waves increased in voltage; in others, they decreased. A few showed changes in the RT intervals in the negative direction to 1.0 mm. below the iso-electric line. A few showed slight changes in the electrical axis. In none of these subjects was the direction of the T-wave changed, nor did we find any of the changes in the chest lead described in our angina pectoris patients during induced attacks of pain.

Method of Study

Any method used for the study of pain and other symptoms in patients with coronary disease or allied conditions of myocardial ischemia should be reasonably accurate and as nearly free as possible from untoward effects.

Such a method of study we believe available in the use of the so-called "Standard Two-Step," utilized originally by Master and Oppenheimer [23] in a study of the response of pulse and blood pressure to a standard amount of exercise. It was used later by Riseman and Stern [24] in their studies on the amount of work required to produce attacks of angina pectoris.

The apparatus used is a two-step staircase. This apparatus has many advantages. The exercise of walking up and down steps is a familiar one and requires only brief directions. The amount of exercise can be readily varied and regulated. If the patient should develop any symptoms, the activity can be immediately stopped and the patient rested and studied in the very room in which the exercise is performed. Its comparative mobility, low cost, and ease of storage are additional advantages for the physician in private practice. The number of foot pounds of work performed may be estimated roughly by multiplying the patient's weight by the height of the staircase (1½ feet) and the number of trips performed (a trip consisting of a single ascent and a descent). This is inexact, however, for it ignores the work done in descent of the stairs. We have been able to confirm by repeated tests the relative constancy of effort required to produce the earliest symptom of discomfort in the individual exercised. Patients were never told their exercise tolerance. In this way the element of suggestion was lessened.

In our opinion the temperature of the ordinary office does not vary sufficiently to affect materially the amount of work necessary to produce discomfort. Wayne and Graybiel [25] also indicate that the temperature of the environment is not a very important factor. Riseman and Stern, however, have shown that in some patients a low environmental temperature is prone to precipitate pain with less effort. This particular point deserves further study in view of recent work indicating the effect of cold on the blood pressure.[26]

Riseman and Stern used as their "end point" the amount of exercise producing sufficient pain to stop the patient. Because of our inexperience with the method and fear of possible danger to the patient, we have taken as our "end point" (after our first few tests) the earliest discomfort indicated spontaneously by the patient.*

* The exact nature of pain production in the heart is not clear. From the work of Lewis, Pickering, and Rothschild [28] one learns that the pain following the contraction of skeletal muscle during ischemia (tourniquet) is associated with actual dilation of blood vessels.

The bulk of experimental work favors the view that pain is due to chemical irritants arising from reduction or cessation of blood supply. Briefly summarized, the evidence for the so-called "ischemia theory" follows:

(1) Ligation of a coronary artery branch results in changes of electrical potential in the area affected and produces characteristic changes in the electrocardiogram.[29, 30] When the arteries studied are only clamped, these changes are temporary and are quickly reversed upon restoring continuity of the artery.[31, 7] The changes referred to are greater inversion of previously negative T-waves in some experiments and the production of a high take-off in the ST complex in others. In unanesthetized animals objective evidence of pain occurs.[32, 33]

(2) Similar electrocardiographic changes occur during attacks of angina pectoris and disappear between attacks.[3, 20]

Three possibilities present themselves:

(1) That lack of oxygen is itself the stimulus,
(2) That some condition resulting from anoxemia is the stimulus,
(3) That irritable substances resulting from the metabolism of muscle, which are not washed away for lack of blood, constitute the stimulus.

The theory that pain is related in some way to anoxemia is supported by the following:

(1) Attacks of pain occur in conditions in which the oxygen content of the blood is low as in anemia [34] or in carbon monoxide poisoning.[35]

(2) Angina pectoris frequently occurs in the presence of aortic insufficiency (low diastolic pressure) or in patients known to have had coronary thrombosis.

(3) Attacks of pain can be induced in susceptible subjects by rebreathing low oxygen mixtures or by strenuous exercise which creates a state of anoxemia generally referred to as "oxygen debt." [19, 36, 37, 38] Such attacks have been found to produce characteristic electrocardiographic changes resembling those following coronary occlusion. Katz,[32] however, has demonstrated that the electrocardiographic changes and production of pain do not necessarily go together. For in many instances exercise or relatively low oxygen mixtures caused the electrocardiographic changes without pain in normal subjects or even in patients with a history of anginal attacks.

Lewis [39, 28] concluded after studying the development of pain in contracting skeletal muscles:

(1) That special metabolic products (P-factor) formed by contracting *but not* by resting muscles stimulate pain endings;
(2) That the locus of their action is in connective tissue and not within muscle cells; and
(3) That the chief value of a good circulation resides in its ability to flush these substances away and not in its ability to supply oxygen. However, Kissin [38] offers evidence that oxygen lack may be an important factor in the production of pain. He observes that anoxemia produced by breathing low oxygen mixtures reduced the time necessary to produce pain in an exercising limb but the degree of anoxemia had to be rather severe in order to become a factor in the production of pain in an exercising muscle.

Katz [32] concludes: "It would appear that the stimulus for pain is a metabolic product (or products) which can readily diffuse into the blood stream and which can be quickly altered in the presence of an adequate supply of oxygen. The accumulation of this product is dependent upon the amount and character of the physiological work and the efficiency on the one hand, and the quantity of oxygen and blood supply on the other. When this substance reaches a concentration above the threshold of the pain end organs, pain results. The chemical product appears to be acid in character, or at least one that is additive with acid substances and is 'neutralized' by alkaline substances. In all probability it is some substance like lactic acid or phosphoric acid formed during the catabolism of muscular activity."

Riseman and Stern studied over 500 induced attacks in 57 patients diagnosed as suffering from angina pectoris. No untoward effects were discovered from the exercise or the induced attacks. Other factors affecting the amount of exercise required to produce pain in a given individual were found to be excitement, recent ingestion of food, previous medication (nitrites), recent attacks of pain, and recent exertion. Thus far we have studied 94 attacks in 40 patients by this method. None has experienced any inconvenience or ill effect, and all have expressed willingness to repeat the test. In every instance the symptoms lasted less than four minutes and disappeared spontaneously.

In addition to determining the amount of exercise necessary to produce discomfort in these patients, we have also observed the effect of the exercise and resulting pain on the electrocardiogram, conventional three leads as well as chest lead. The position of electrode on the chest was marked and the identical area used in the subsequent tests.* In all instances an electrocardiogram was taken after a rest period of 30 to 60 minutes. The importance of this rest period is pointed out by Duchosal and Henny [6] who made the following interesting observation. An electrocardiogram was taken of a patient after a night's rest in bed. During the next hour and 25 minutes, the patient was permitted to walk around his bed a few times, following which he rested 35 minutes. Another electrocardiogram was then taken. No pain occurred during the two hour interval, yet the second electrocardiogram showed a distinct drop of the T-wave and a slight drop of ST when compared with the earlier (basal) electrocardiogram. We feel that it is desirable to use the same basal conditions as for metabolic determinations.

The speed of the string type electrocardiograph made it preferable for our studies. Not infrequently, we have been able to take a four lead electrocardiogram (standard leads and one chest lead) in 75 seconds (10 to 12 cycles per lead) whereas trials with two of the older amplifier type machines required from six to ten minutes for similar determinations. Both timings were made with the electrodes attached to the subject and, in the case of the amplifier type machine, after the current had been turned on for a sufficient period. The time loss is due to oscillations of the light beam as connections are made for the various leads. In some of the newer amplifier machines, this difficulty seems partially corrected. Ease of standardization is an advantage of the amplifier type apparatus.

The necessity for speed arises from the importance (emphasized by Scherf [27]) of comparing with the resting electrocardiogram the tracings taken immediately after exercise and at stated intervals following. The advantage of speed of operation is well illustrated in the electrocardiograms of our first patient. (Figures 1 *A* and *B*.) Significant changes were seen

* The right arm electrode was held at the left fourth intercostal space near the sternal border and the left leg electrode used as the indifferent electrode.

in the tracing taken immediately after exercise. The tracing taken five minutes after exercise disclosed only insignificant changes with reference to the resting electrocardiogram, considering that inversion of T_3 may occur in normal subjects after exercise.

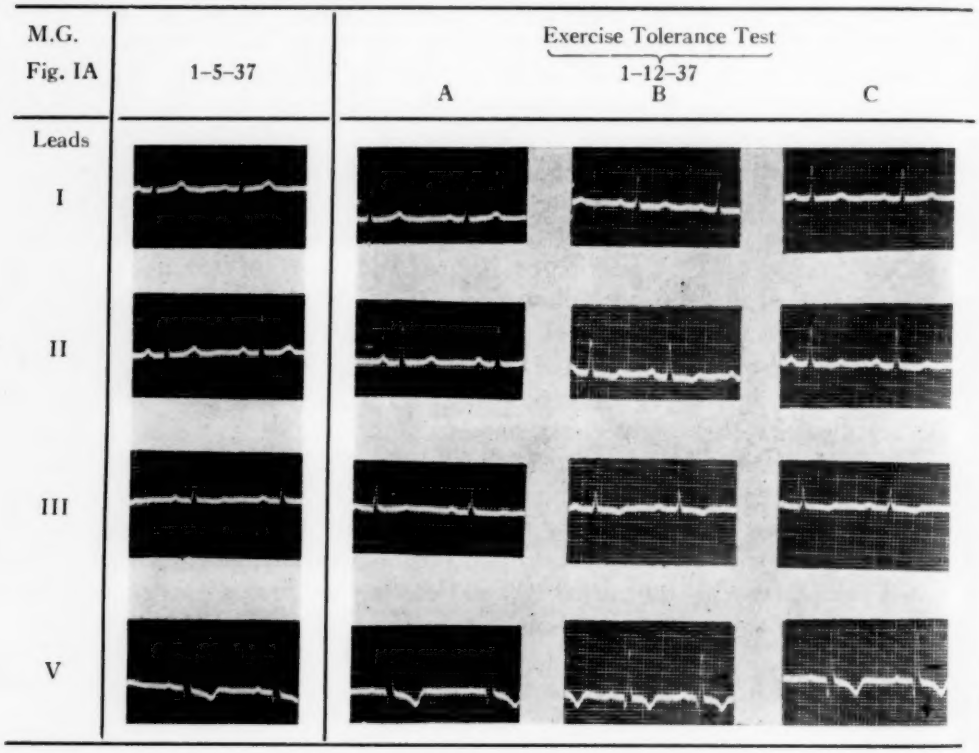

FIG. 1-A. *January 5, 1937.* Routine electrocardiogram shows no preponderance of either ventricle, normal T-waves, and normal RT intervals. Rate is 60. PR measures 0.20 second. Normal chest lead.

January 12, 1937. Exercise tolerance test shows:

A. Resting electrocardiogram is identical with the tracing taken on January 5, 1937. Rate is 60.

B. Electrocardiogram taken immediately after exercise, consisting of 27 trips on the standard steps in 2½ minutes. Rate is 68. Note changes in T_2 and T_3. T_3 has become diphasic and RT_2 has dropped below the iso-electric line. T_2 has become inverted. T_2 has dropped to 1.0 mm. The chest lead shows very little change from the chest lead of the resting electrocardiogram. The T-wave in this lead reaches but 2.5 mm. below the isoelectric line as compared with 4.0 mm. in the resting tracing.

C. Electrocardiogram taken five minutes after the exercise was finished. Rate remains at 68. The tracing has almost returned to the resting appearance. Note the return of RT_2 to the isoelectric line. T_1 is still lower than in *A*. The chest lead is identical with the one in *A*. The location of the chest electrode is the same for electrocardiograms *A*, *B*, and *C*.

Electrocardiograms of Patient M. G. All electrocardiograms have been taken with the standardization of 1 cm. equal to 1.0 millivolt. The connection for Lead V is made between the electrode placed at the left sternal border and the left leg.

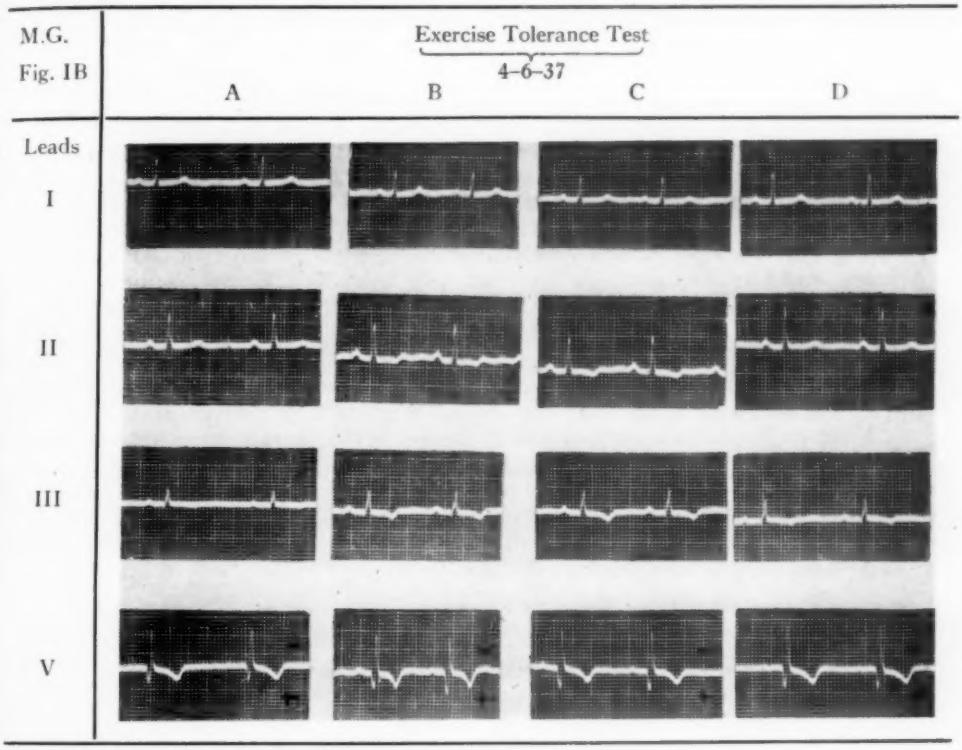

FIG. 1-B. *April 6, 1937.* Exercise tolerance test shows:

A. Resting electrocardiogram. Rate 54. Sinus bradycardia. PR measures 0.22 second. T_1 measures 1.2 mm. T_2 measures 1.0 mm. The chest lead is within normal limits.

B. Taken immediately after 23 trips on the standard steps. No symptoms noted as a result of the exercise. Rate rose to 66. T_1 remains unchanged. T_2 is diphasic and associated with a lowering of RT_2. T_3 is sharply inverted. The chest lead is unchanged.

C. Electrocardiogram taken three minutes after the exercise. No change in rate. More marked changes in T_2 and T_3. T_1 is also slightly lower.

D. Electrocardiogram taken 10 minutes after the cessation of exercise shows a return to the resting electrocardiogram. (See electrocardiogram *A* above.)

CLINICAL APPLICATION OF WORK TESTS

Case History 1—Showing marked electrocardiographic changes after slight exercise without production of pain. Patient has coronary disease, a low basal metabolism, and a hyperchronic anemia.

Miss M. G., a 56 year old graduate nurse, presented herself for examination on March 18, 1937, because her "heart was not strong enough to carry on." Although she considered that the onset occurred suddenly in April 1935, during a period of great anxiety and overwork, closer questioning revealed that for 10 years she had had a "fatigue pain" under the left scapula. This was definitely related to overexertion; it would occur at the height of activity, and disappear after one-half hour's rest.

One night in April 1935, she noted an irregular beating of the heart and a "fear of sudden death." Pain suggesting the acute closure of a coronary artery was not noted. Also about this time she was awakened by severe dyspnea. This was immediately and completely relieved by standing. Although she was able to assume her duties that day, her physician insisted upon her staying away from work for a period of time. She remained at home for 11 weeks, but during this time the re-

sponsibilities of caring for an invalid father interfered with rest. About the same time there occurred a gradual change in the back discomfort. This " fatigue " pain now would radiate to the left breast and substernal region. Nitrites have never been used.

Of interest in the past history was an anemia discovered in 1928 (red cells, 2,800,000; hemoglobin, 50 per cent). Her basal metabolism was 4 plus. A gastrointestinal roentgen-ray series was negative. Cholecystograms were not made.

For the past two years she has had great difficulty keeping warm and would use hot water bottles in bed. At night twitching of the feet and thighs disturbed her.

Since 1934 she has taken thyroid extract gr. ½ (0.03) (Parke-Davis) daily and a preparation of liver extract. A blood count on 3–30–37 was reported: hemoglobin, 86 per cent; red cells, 3,999,000; and white cells 5,400. Another on 1–30–38 showed: hemoglobin, 73 per cent; R.B.C. 3,900,000 and the smear showed macrocytosis, anisocytosis and a rare basophilic red cell. A gastric analysis has not been done because of the underlying cardiac condition. The patient has recently been started on dilute hydrochloric acid with meals and injections of a potent liver preparation.

Physical examination showed: Weight was 177½ pounds. Height was 59½ inches. There was a slight yellowish tint of the skin, but no signs of myxedema. The ocular fundi were negative. The peripheral arteries were soft. Blood pressure was 134/80. The heart was normal in size both on physical examination and by roentgen-ray. The lungs and abdomen were negative.

Her basal metabolic determinations are listed:

Date	Basal Rate	Remarks
4– 9–37	−40%	Thyroid omitted for 10 days
4–23–37	——	Started thyroid (Armour's) gr. I (60 mg.) daily
5– 7–37	−40%	Taking thyroid—same dose
6– 4–37	−36%	Taking thyroid—same dose
7–10–37	−31%	Taking thyroid—same dose. Feeling much better
9– 2–37	——	Exercise test
9– 4–37	−33%	Same dose thyroid
12– 4–37	−31%	Improvement maintained. Thyroid reduced to gr. ½ (30 mg.)
1–28–38	−35%	Feeling about same. On same dose thyroid
2– 1–38	——	Exercise test

Other laboratory findings were: Blood calcium was 10.8 mg. per cent; phosphorus, 3.1 mg. per cent; cholesterol, 625 mg. per cent and N.P.N., 37 mg. per cent. Blood Wassermann and Kahn tests were negative.

Resting electrocardiograms taken at intervals since March 1935 had shown inconstantly a slight prolongation of auriculo-ventricular conduction to 0.22 second. Lead V was normal. Because her symptoms so overshadowed the objective findings, we obtained permission from Dr. B. J. Slater to make exercise studies. In this we received the hearty coöperation of the patient.

Exercise Tolerance Tests

Date	No. of Trips	Time	Remarks
1–12–37	27	2½ minutes	No pain felt. Admitted some dyspnea after questioning (figure 1 *A*)
4–6–37	23	2¼ minutes	No pain or dyspnea (figure 1 *B*). (Test taken to study the changes in the absence of pain.) (BMR—40 per cent)
9–2–37	23	2¼ minutes	Patient asked to stop the test because of marked chest pain. Had taken desiccated thyroid for 2 months. (BMR—31 per cent,—33 per cent)
2–1–38	25	2½ minutes	Slight shortness of breath. Patient asked to stop because
	29	2¾ minutes	of tightness in chest. No pain or objective dyspnea

Although compatible with a diagnosis of coronary artery disease, this patient's history was remarkable for the meagerness of objective evidence implicating the circulatory system. It is probable that her anemia contributed greatly to her cardiac symptoms and that her marked symptomatic improvement during the past six months may be partially explained by the increased oxygen carrying capacity of the blood, consequent to the improvement of the anemia. The anemia itself may be partially the result of hypothyroidism. The cardiac symptoms in the presence of a low metabolic rate deserve comment in view of the recent vogue for completely removing non-toxic thyroid glands. These operations have been done on other patients in an attempt to establish clinical improvement by decreasing the demands on the circulatory system. Our patient's problem is further complicated by the possibility of inducing more cardiac symptoms if the metabolic rate is increased by the administration of thyroid substance. On the other hand, some of her cardiac symptoms may be the result of hypothyroidism. The transient changes in the T-waves and RT intervals of Leads II and III seemingly give objective evidence of impaired coronary circulation.

On June 4, 1937, her basal metabolic determination was minus 36 per cent after having taken desiccated thyroid 30 mg. (gr. ½) daily for three weeks. Upon resuming this medication, she felt improved. The dose was then increased to 60 mg. (gr. I) daily with subjective improvement, although the patient was still having some cardiac symptoms particularly at night. On September 2, 1937 there was apparently a decrease in her exercise tolerance, in that after 23 trips she asked to stop by reason of pain. This is comparable with Blumgart's [42] experience with patients who developed myxedema after total thyroidectomy for angina pectoris. Relatively small doses of desiccated thyroid substance were sufficient to diminish the gains in exercise tolerance made through the operation.

Case History 2—Illustrating the effect of exercise on the electrocardiograms of a patient with a duodenal ulcer and coronary artery disease complicated by a marked anxiety neurosis.

The patient, Mr. A. T., a 43 year old clothing designer, was referred by Dr. Ellis B. Soble and Dr. George R. Lavine for cardiovascular study.

The important points obtained from Dr. Soble's record follow: Since 1932 the patient had complained of substernal and epigastric pain. History taking had always been affected by his extreme suggestibility and tendency to phobias. The onset of symptoms was sudden, immediately following the death of a friend from heart disease. The discomfort occurred after eating, was relieved by eructation, and was not affected by exercise. Relief was sometimes obtained by an enema. His general physical examination was negative, and the blood pressure varied from 140 systolic and 80 diastolic to 160 systolic and 100 diastolic. Gastrointestinal roentgenological studies showed evidence of duodenal ulceration. Marked relief was obtained by the administration of a bland diet and alkali; although, for a short while, he continued to have some of the discomfort in his chest. He was free from precordial discomfort until November 1935, when it recurred for a short time with numbness of the left arm. Throughout this period, the patient had been difficult because of hysterical symptoms. He remained relatively well until July 1936, when there occurred a sudden attack of severe epigastric pain. A diagnosis of perforated ulcer was made and

confirmed by operation. A resection was done, and convalescence was uneventful. In January 1937, his only complaint was "heart ache." The patient was uncertain whether or not he obtained relief by nitroglycerine. It was because of the persistence of these symptoms that he was referred to us for further study.

An insight into the psychiatric background was given by Dr. Lavine who summarized his studies as follows: The patient has always been shy, seclusive, and self-conscious. In his earlier years he had been protected by an older brother. After the brother's death, he became fearful and developed "shaking spells." He was irritable, apprehensive, and had definite sexual disabilities. He also had a fear of developing insanity. Since the sudden death of his friend, the patient thought that he had heart disease.

We first saw him in May 1937, and at that time he described the occurrence one week before of a pain in his left shoulder, numbness of the left arm, a "heaviness" over the upper sternum, and a tightness in his throat. Partial relief was obtained by resting; but greater relief was experienced after drinking a glass of water. It was hard to get a clear appraisal of his symptoms because of his proneness to contradict himself.

Since his operation eight months before, he had been conscious of hyperesthesia of the left shoulder region. In the morning when stooping to pick up his shoes, he would note a "cramp" in his left shoulder. The symptom, however, might occur at any time by "thinking about it." It was also noted in the morning when walking 15 yards to his garage. Bending to enter the car would increase the pain near the distal end of his left clavicle. It would radiate to the suprasternal notch and interscapular region and would last for 15 minutes. It was unaffected by breathing and was partially relieved by eructation or taking soda bicarbonate. The patient was not certain that nitroglycerine gave any relief, nor was he certain that he could produce the symptom by walking any other time of the day. He had been able to continue his daily work and apparently had very little difficulty except for the short period after breakfast.

His physical examination was essentially negative. The blood pressure was 146 systolic and 80 diastolic. The carotid sinus reflex was very active. Fluoroscopic examination of the chest was negative.

A single resting electrocardiogram, taken on May 8, 1937, showed very little change from the normal. The patient had experienced a severe pain two hours before the tracing was taken. T_1 was slightly diphasic, but it would be difficult to rule out the presence of a U-wave. The slight depression of RT_3 would not be given much significance by most clinicians. The presence of the diphasic T-wave in the chest lead is a possible deviation from the accepted normal.

Edeikin, Wolferth and Wood [40] offer evidence that a diphasic T-wave in the chest lead or an upright T-wave in this lead are suggestive of heart disease. However, because many patients showing such borderline changes in their electrocardiograms are free from symptoms of cardiac disease and because of the extraordinary combination of gastrointestinal, cardiovascular, and mental symptoms in one patient, we felt it important to obtain as much objective evidence as possible.

It was with this in mind that we determined to study the effect of exercise. On June 5, 1937, two hours after a very light lunch and one and three-quarter hours after resting in recumbency, his basal electrocardiogram (A) was taken following which he was exercised at the rate of 12 excursions per minute.

Elapsed time in minutes	No. of trips	Remarks
0	27	"A little pain"
	34	(Pointing to left shoulder) "not bad"
	43	"Getting worse"
3:45	44	Exercise stopped

The electrocardiograms taken before exercise (figure 2) on June 5, 1937, showed no deviation from the normal in the standard three leads. However, T_5 was diphasic. Electrocardiogram B started 75 seconds after the cessation of exercise, showed a drop in voltage of T_1, a depression of RT_2 and RT_3, and a change of T_2 and T_3 from positive to diphasic waves. The

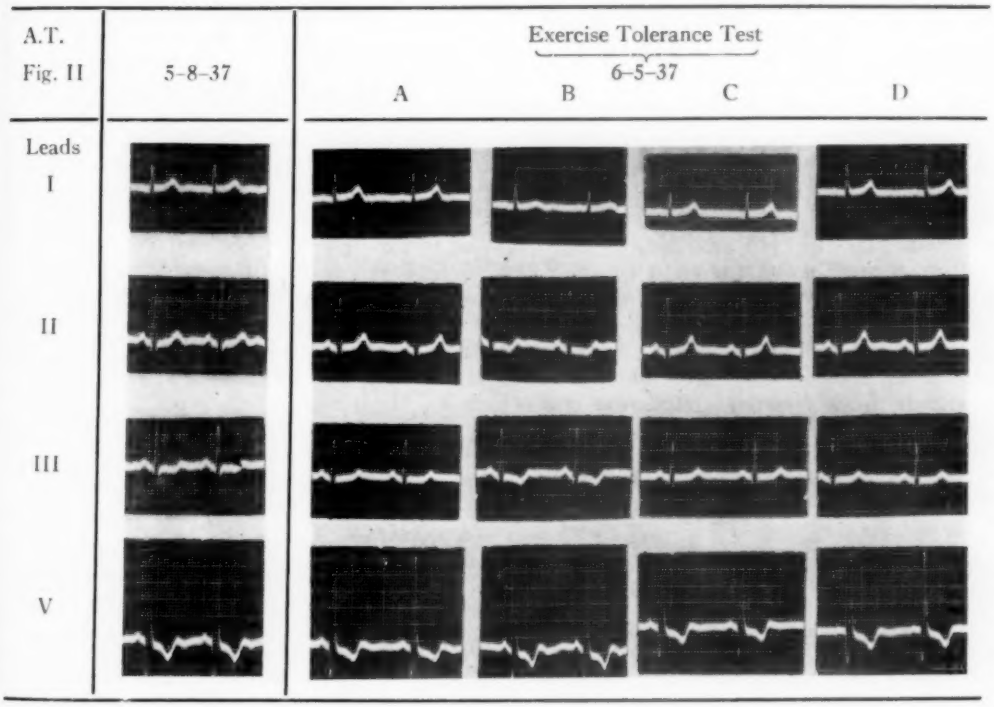

FIG. 2. Electrocardiogram of Patient A. T.

May 8, 1937. Rate, 72. Slight depression of RT_3. T_1 is slightly diphasic. Patient had severe spontaneous attack of pain two hours before this electrocardiogram was taken. The chest lead shows a diphasic T-wave.

June 5, 1937. Exercise tolerance test shows:

A. Resting electrocardiogram shows normal three conventional leads and diphasic T_5. Rate is 65.

B. Electrocardiogram taken 75 seconds after exercise. Rate is 60. T_1 has dropped and is slightly diphasic. T_2 and T_3 have become diphasic and are associated with a drop of the RT interval. The chest lead remains unchanged.

C. Electrocardiogram taken 10 minutes and 15 seconds after exercise. The tracing has almost returned to *A* above. Rate is 58. T_1 is still slightly lower than T_1 in *A*.

D. Electrocardiogram taken 16 minutes after exercise shows no change from *A*.

chest lead showed no significant change from the resting one. In electrocardiogram C, started 10 minutes and 15 seconds after the cessation of exercise, one notes almost a return to the resting electrocardiogram. T_1 is still a little lower than in electrocardiogram A. Electrocardiogram D, taken 16 minutes and 15 seconds after the cessation of exercise, duplicates the resting electrocardiogram.

The transient changes in the standard leads taken immediately after exercise would seem to give objective evidence of "myocardial ischemia."

Case History 3—Showing the effect of exercise on the electrocardiogram of a diabetic with symptoms of coronary disease. A routine electrocardiogram was essentially negative; the exercise test showed changes most marked in the chest lead.

Mr. E. C., a 46 year old tailor, was first seen on August 15, 1936, because of "back pain" and a "tight feeling" in his chest if he walked one block. His symptoms started gradually three years before. However, following the discovery of diabetes mellitus in 1934 and its control by diet, he felt well until four months before his first visit to our office. At that time, while ascending a flight of stairs, he experienced a sudden pain in his left scapula. Because this persisted for 24 hours he visited a physician, who baked and massaged his back. The pain was also noted over the front of his chest, more on the left than right side. He continued to work, although throughout that week he had the same discomfort every morning after ascending one flight of stairs, or if he walked more than one block. The discomfort would start in both scapulae, radiate over the top of the two shoulders to the left breast, and then to the right breast. At such times he became dyspneic and had to stop. His diabetes has remained under control by dietary means alone.

Physical examination showed his weight to be 171 pounds. Height was 5′ 2¾″. Blood pressure was 132/80. The peripheral and retinal vessels were normal. Heart sounds were distant and the rate was 80. The heart was otherwise negative. Rhythm was regular. Moderate emphysema of the lungs was present. The abdomen was negative.

Laboratory tests showed the following: Blood sugar (mid-afternoon) three hours after a meal was 112 mg. per cent. Blood Wassermann and Kahn tests were negative. Hemoglobin was 97 per cent. Red blood count was 5,500,000. White count was 5,800.

His exercise tolerance tests indicating the number of trips required to produce pain are shown in the table on page 2031.

It has been the experience of others (Riseman and Stern) that within limits the exercise tolerance is quite constant, and this was confirmed by our experience with a smaller series. Also, Brown and Riseman [41] have shown that an increase in exercise tolerance of 50 per cent or more usually caused a striking diminution or complete absence of attacks in daily life. Our protocol confirms the increase in exercise tolerance commented upon by Riseman and Brown in one of their recent papers [43] in which they described the beneficial effects of nitroglycerine and also xanthine derivatives on many of their angina pectoris patients. We heartily agree with their statement, "If medication induces improvement in a patient who has attacks on exertion, this improvement should be evidenced by an ability to perform more work than was possible without medication." In the protocol above on 11–20–37, it seems quite conclusively shown that for all practical purposes the effect of

Exercise Tests

Date	Remarks	No. of Trips‡ to Produce Pain
9–11–36	Phyllicin* started	19
9–28–36	Subjective improvement noted. Placebo substituted (Soda mint)	34
10–31–36	Not feeling as well as with Phyllicin. Placebo stopped. Theocalcin† started	28
12– 5–36	Feeling about same. Theocalcin stopped. Nitroglycerine started thrice daily before meals and p.r.n.	27
8–21–37	Subjectively much better. Last dose of nitroglycerine 4 hours before test. Using only one dose in a.m. and free from discomfort rest of day. Walks home 5 blocks	27
9–10–37	Much subjective improvement since last visit. Same regime	30
11–20–37	Feeling about same. Last dose nitroglycerine *1 hour* before test.	
	Pain lasted 3 minutes	32
	Allowed to rest 20 minutes and given nitroglycerine. Test started 3 minutes later	70
	Patient stopped exercise chiefly because of leg pains. Had only slight precordial pain	
1– 8–38	Not doing as well. Glycosuria present. Phyllicin started again	24
1–29–37	Clinically much improved. Able to walk 7 or 8 blocks without pain.	
	Pain started at	30
	Pain moderately severe at	36
	Electrocardiogram taken	

* Theophyllin—Calcium Salicylate.
† Theobromine—Calcium Salicylate.
‡ Rate 12 to 14 trips per minute.

nitroglycerine had ceased before the first exercise test was performed, and that following its administration the exercise tolerance increased by almost 120 per cent.

The changes in the electrocardiograms (see figures 3 *A* and B) are reflected chiefly in the chest Lead (V). We have not encountered in any of our normal controls after exercise the change from the normally inverted T-wave in the chest lead to one that is diphasic, preponderantly positive, and associated with an elevation of the RT interval above the iso-electric line as demonstrated in this patient.

On the basis of this patient's symptoms and the transient changes in his chest lead after exercise, we made a diagnosis of coronary disease. We suggest that such changes in the chest lead after exercise may be considered evidence of myocardial ischemia, even though the conventional three leads remain normal.

Discussion and Conclusions

The earliest use of the electrocardiograph was directed to the analysis of abnormalities of rhythm and rate. As experience was gained, it was found that valuable information about myocardial function was obtainable from a study of the shape, amplitude and time relations of the individual deflections. In more recent years the use of chest leads has frequently supplied information not obtained from the conventional three leads. However, in many

patients with definite impairment of myocardial circulation, all routine clinical tests may yield negative results.

Methods are discussed for obtaining objective evidence of myocardial ischemia (angina pectoris)—where the diagnosis would otherwise rest solely upon a more or less ambiguous history—by comparing electrocardiographic tracings, after rest, immediately after a measured amount of exercise, and at successive intervals after the exercise, using chest leads as well as the conventional three leads. We have been able to confirm the significance of the transient changes in the T-waves and RT segments described by other workers.[3-20] Particular importance is attached to including

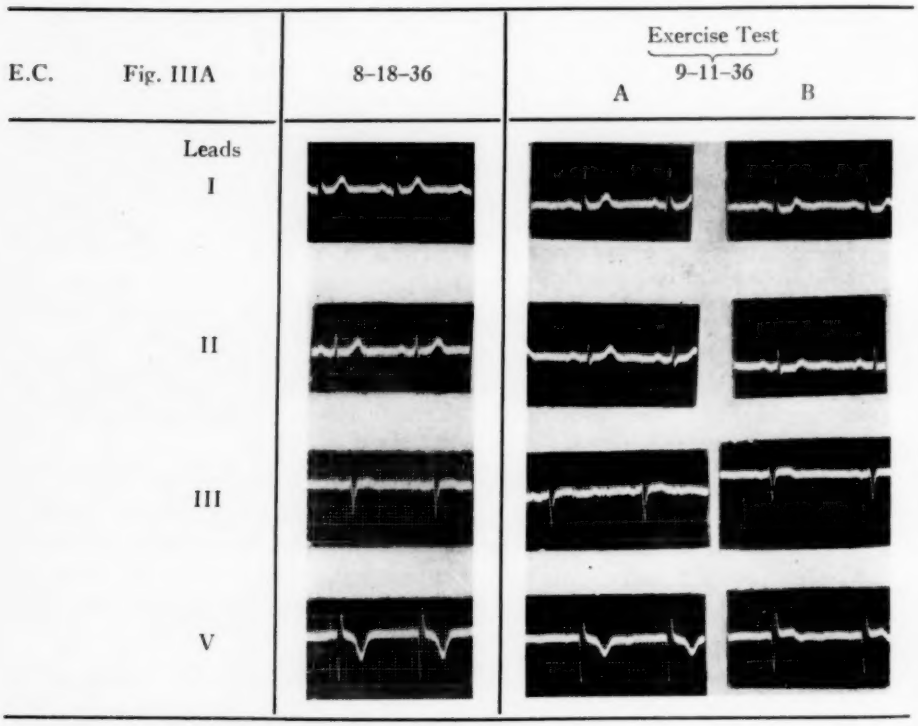

FIG. 3-A. Electrocardiogram of Patient E. C.

August 18, 1936. Resting electrocardiogram. Rate 58. Normal T-waves and RT intervals. Slurring and notching of QRS in all leads. Left axis deviation. Deep Q_3.
September 11, 1936. Exercise test shows:

A. Resting electrocardiogram which is almost identical with the one taken on August 18, 1936. T_3 reaches but 3.5 mm. below the iso-electric line in contrast with 6.5 mm. below the iso-electric line in the tracing of August 18, 1936. This difference in the T-wave may be the result of a change in position of the chest electrode. The rate is 53.

B. Electrocardiogram taken immediately after 19 trips on the standard steps. Rate 50. RT_1 and RT_2 are slightly lower and T_1 and T_2 have dropped slightly in voltage. In Lead V there is seen a distinct change in direction of the T-wave which is now upright and associated with a high take off of the RT interval. The chest electrode was placed in the identical area as in electrocardiogram *A*.

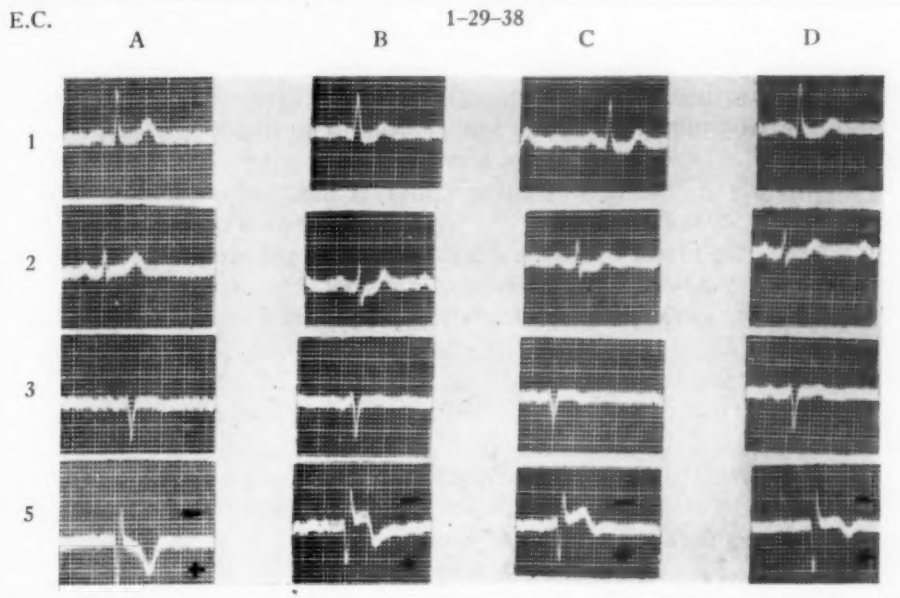

FIG. 3-B. Electrocardiograms of Patient E. C., January 29, 1938.

A. Resting electrocardiogram. Nitroglycerin 6½ hours before. No significant change from resting electrocardiograms on August 16, 1936 and September 11, 1936. Rate, 52.
B. Electrocardiogram after 36 trips. Finished two minutes after cessation of exercise. Rate 85–62. Observe negative shift of RT–1 and 2 and upward (negative) shift of the RT interval in the chest lead with a change in direction of T.
C. Started two and one-half minutes after *B* and finished in 85 seconds. Rate, 65. Changes still persist in Leads I and II and are slightly less distinct in the chest lead.
D. Started two minutes after *C* (seven minutes after exercise ceased) and completed 75 seconds later. Rate, 62. Shows less marked changes in Leads I, II, and V.

the chest leads, since they sometimes yield positive information after exercise when the conventional three leads are negative. We have not encountered in any of our normal controls after exercise the change from the normally inverted T-wave in the chest lead to a diphasic or upright one with elevation of the RT interval nor have we noted the disappearance of the Q-wave in the chest lead after exercise. We believe that these changes may be considered objective evidence of myocardial ischemia. Electrocardiographic changes may occur after exercise even in the absence of pain production. (See Case History 1.)

It is *not* to be assumed that negative results after the application of these tests disprove the existence of angina pectoris in the face of a history indicating its possible presence. At the present time it cannot be said that the tests have negative significance.

The tests are deprived of value unless the basal electrocardiogram is taken after adequate rest. Otherwise the contrast between rest and exercise is upset and the exercise administered is cumulative and incapable of

being accurately measured. At best there is only an approach to precision. For that matter, adequate rest is equally important before taking a routine electrocardiogram. The mechanism of individual cardiac attacks deserves study by this method also because in certain subjects these attacks may be the result of arrhythmias which, if recognized, may respond to appropriate therapy.

The history of the patient often indicates the approximate amount of exercise that can be tolerated. The work performed was measured on the "Standard Two-Steps," a method sufficiently simple and accurate to lend itself to clinical application. Such determinations may, of course, be made without observing the effect on the electrocardiogram. The methods used afford a possible means of observing the effect of therapy or the course of the morbid condition itself, inasmuch as a series of tracings, before and after exercise, may show changes where a series of tracings taken at rest do not.

In interpreting the tracings, it must be borne in mind that the mere fact that some changes appear does not necessarily indicate abnormality, since certain changes occur in normal subjects.

The coincidence of transient changes in the electrocardiogram with symptoms may in the selected atypical case establish a diagnosis otherwise uncertain (see Case History 2).

This method has proved entirely safe when the patient was admonished to stop on feeling any appreciable discomfort. Furthermore, in the hands of others, even when the exercise is carried to the point of causing pain severe enough to stop further activity, there have been no untoward results.

We wish to express our sincere thanks to Mr. Arthur E. Rosenberg for his assistance.

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CASE REPORTS

A CASE OF CHRONIC HEMORRHAGIC BRIGHT'S DISEASE ASSOCIATED WITH AN ANOMALOUS BASOPHILIC PITUITARY GLAND *

By Raymond F. Holden, Jr., *New York, N. Y.*

It is the purpose of this report to present a case of chronic hemorrhagic Bright's disease in which a remarkable pituitary basophilism apparently contributed to the clinical picture.

F. B., an unmarried Jewess of 30 years, referred by Drs. J. Eidelsberg and J. W. Wilner of New York City, entered the Rockefeller Institute Hospital May 11, 1935, with complaints of swelling of the face and lower extremities, increasing weakness, and failing vision for one and one-half years; also obesity and diabetes for 10 years.

Family and Personal History. The patient was one of a family of four children; her three sisters were healthy. Her family history was notable in that both grandmothers had diabetes; her mother had suffered from nephrolithiasis for 13 years; while her father, a mild diabetic, was at the time confined to bed by a hemiplegia.

Her health, up until 10 years before admission, had been fair. She had measles, scarlet fever, and diphtheria during childhood without obvious sequelae. A marked myopia had been present since infancy. She had been classed as mentally retarded in school and did not finish the eighth grade. Her occupations had included millinery, clerical, and household work.

The onset of catamenia was at 13 years. Menstruation had been normal until the past two years, when it had become scanty and irregular.

About 10 years ago she had suddenly grown excessively fat. Shortly after this, a diagnosis of diabetes had been made. She had followed dietary restrictions in desultory fashion and during recent months had taken from 10 to 20 units of insulin daily.

Present Illness. Edema appeared first in November 1933, following a cold. During the following six months she gained 20 pounds in weight. She entered the Post-Graduate Hospital in November 1934. A diagnosis of chronic nephritis was made and a high-protein, low-salt diet was prescribed. Her weight fell from 200 to 159 pounds during her three weeks' stay in the hospital. On discharge she was instructed to continue the diet and 20 units of insulin daily for the diabetes. Thyroid was administered for a short time, but it produced severe muscular cramps and had no effect on the edema. She neglected her diet and began to gain weight again, so that she weighed 198 pounds on admission to The Rockefeller Hospital.

Physical Examination. The patient was an obese young woman with generalized anasarca. Her face was so swollen that the palpebral fissures were closed, while her lower extremities exhibited massive edema. The skin of her neck hung in folds and the breasts were extraordinarily large and pendulous. Aside from the dependent edema, her appearance was rather similar to the photograph of Case 2 in Cushing's series (Cushing (1932), p. 151). There was a myopia of 10 + D., which made examination of the fundi difficult. Retinal arteriosclerosis, scattered hemorrhages, and deposits of exudate were noted. There was a pronounced upper dorsal

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From the Hospital of The Rockefeller Institute for Medical Research, New York,

kyphosis. Moist râles were heard at both lung bases. The heart was not enlarged by percussion, but the aortic second sound was accentuated and the blood pressure was 224 mm. Hg systolic and 116 diastolic. There were no signs of fluid in the large, flabby abdomen. The liver and spleen were not felt. Pelvic examination revealed a nulliparous cervix with a small amount of mucopurulent discharge; the fundus and ovaries could not be felt. The reflexes were sluggish.

Laboratory Data. Roentgenograms of the heart and lungs demonstrated a relatively small thoracic cage, but no other abnormality. Lateral views of the skull showed a normal appearance of the sella turcica and cranial vault. Electrocardiograms indicated a normal cardiac mechanism with left axis deviation. The basal metabolic rate was plus 20 per cent, presumably due to thyroid taken before admission.

In addition to the data given in the graphic chart, the following laboratory findings were obtained: Blood non-protein nitrogen, 59 mg. per cent; plasma free cholesterol 110 mg. per cent; total cholesterol, 264 mg. per cent; fasting blood sugar 65 mg. per cent. After 100 gm. glucose were taken by mouth the per cent blood sugar values were as follows: 1 hour, 112 mg.; 2 hours, 138 mg.; 3 hours, 99 mg.

Urine from the second half of a 24-hour Addis concentration test showed: Volume 950 c.c., pH 7.0, specific gravity 1.0165 (corrected for protein), protein 7.9 grams per liter (7.5 grams per 12 hours), red blood cells 2.5 million in 12 hours, casts 140,000 (100 per cent hyaline), oval fat bodies. Subsequent laboratory findings are shown graphically in figure 1.

Clinical Course. On the basis of the physical and laboratory findings, a diagnosis of chronic hemorrhagic Bright's disease was made. Single urine specimens showed persistent moderate glycosuria, not affected by administration of insulin, which was soon discontinued. Because of the peculiar obesity, high sugar tolerance, renal glycosuria, and menstrual irregularity a diagnosis of adiposogenital dystrophy was considered. The basal metabolic rate went to plus 43 per cent on a short course of thyroid, and the patient showed no improvement. She complained of constant pain in her thighs, also severe headaches. The blood pressure remained high and fresh retinal hemorrhages appeared. She lost weight (edema) rapidly on a high-protein diet with restricted salt, going from 90 kg. on admission to 70 kg. on discharge six weeks later.

After leaving the hospital she allowed her diet to lapse and began to grow edematous again. At the time of her second admission, three months later, she weighed 94 kg. and appeared in every way the same as when she was first seen. The urea clearance was 12.5 per cent and the blood non-protein nitrogen 73 mg. per cent. On the same diet given previously, her weight fell to 88 kg. during three weeks in the hospital and she was again sent home. Edema returned promptly and she was readmitted a month later in an extremely weakened condition, despite efforts which had been made to provide a proper diet at home. The urea clearance was now 5.6 per cent and the blood non-protein nitrogen 102 mg. per cent. At this time there were definite signs of fluid in her chest. She was again placed on a high-protein, low-salt diet and began to lose weight slowly. Increasing dyspnea and orthopnea set in and it was felt that cardiac decompensation had become a factor. Digitalis was given without any noteworthy effect. She complained of lower abdominal pain and had some vicarious menstruation. Nothing abnormal was noted on pelvic examination. During the following month signs of uremia supervened and she began to vomit with increasing frequency. The urea clearance fell to 2.5 per cent six weeks before death and remained at this level. She suffered a severe attack of secondary glaucoma and her vision failed completely, despite intensive treatment with eserine. Her weight dropped continuously, reaching 66 kg. a week before death. The last complication to appear was a swelling of the right parotid gland, associated with cellulitis of the face and neck.

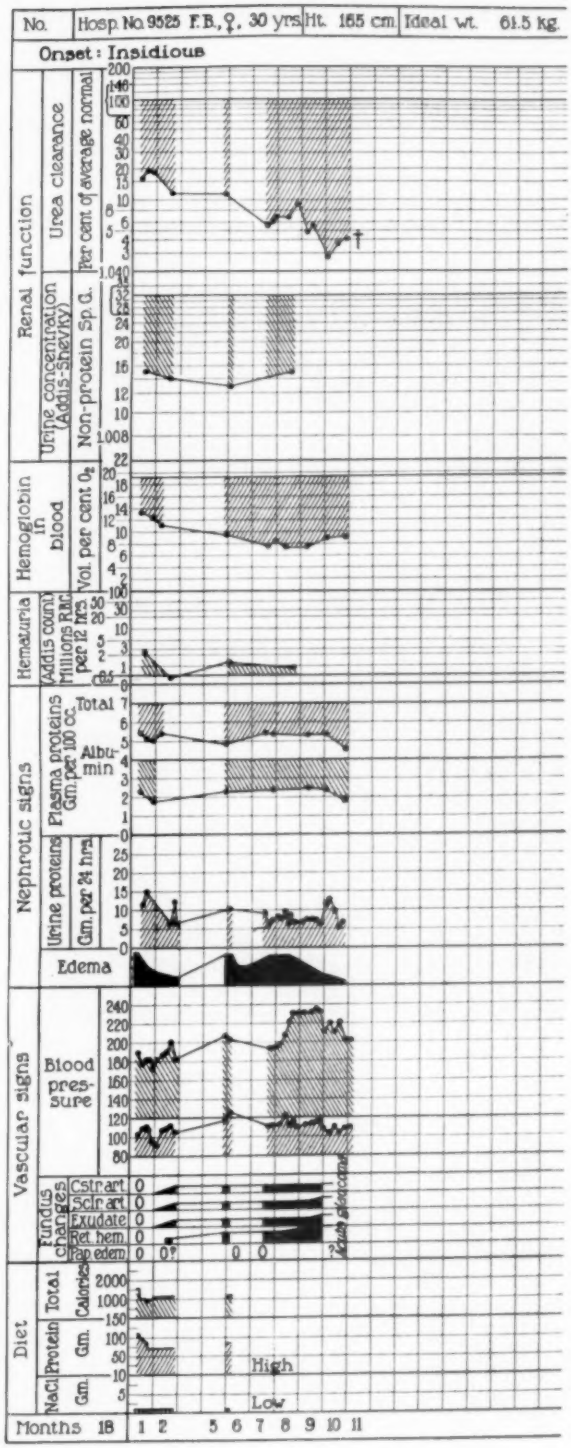

FIG. 1. Chart of the laboratory findings in the patient.

Autopsy. The autopsy was carried out by Dr. C. P. Rhoads, and the following data are from his record.

A remarkable picture was presented by the pituitary gland and its environs (figures 2 and 3). The carotid bulbs extended to above the normal height and approached the midline to such an extent as to compress the hypophysis between them, so that its sides were concave and the antero-posterior diameter extended. The vessels were soft and elastic, without aneurysmal change. Microscopically, the anterior lobe was found to consist almost entirely of basophilic cells, with only a few groups of acidophilic cells. The posterior lobe contained no adenoma and was not otherwise remarkable. The kidneys were normal in size, shape, and consistency.

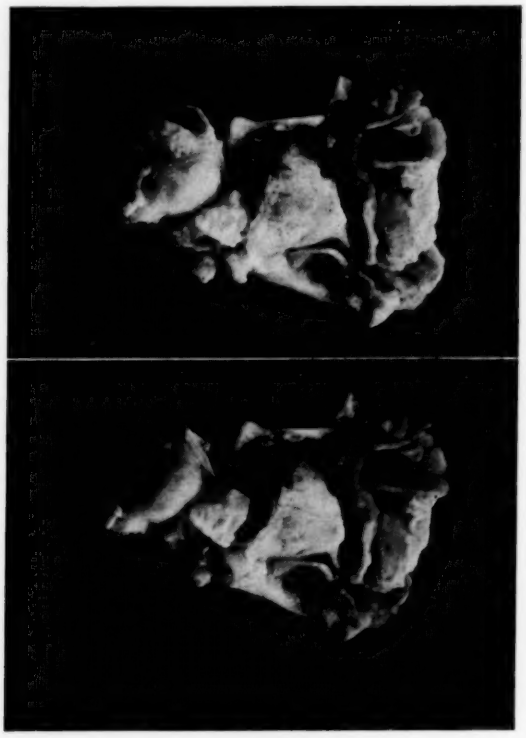

FIG. 2. Photograph showing a dorsal view of the pituitary in the sella turcica. The carotid bulb can be seen on each side of the gland, somewhat separated from it for photographic purposes. The lateral compression and deformity of the gland are well shown.

The capsules stripped easily, leaving mottled brown-yellow surfaces which were slightly irregular. The cortex was of normal thickness on section, but had a peculiar translucent appearance and presented scattered small yellow areas. Many branches of the renal arteries were almost occluded by masses of atheromatous tissue. The pelves and ureters were not remarkable. Microscopically, a very advanced chronic glomerulonephritis was apparent. Hyaline deposits and endothelial proliferation within the glomeruli were present in various stages of development. Fibrin thrombi were seen in some glomerular capillaries. The tubules were dilated and showed widespread degeneration of the tubular epithelium. The interstitial tissue was increased in amount and infiltrated with lymphocytes. Intimal proliferation and atherosclerosis of the arteries were striking. The left ventricle of the heart was

hypertrophied. Atheromatous areas were noted in most of the large arteries; especially in the renal arteries and their branches, the coronary arteries, and the circle of Willis. There were a few fibrous pleural adhesions and the lungs were moist, with frothy fluid in the bronchioles. The liver, spleen, and two accessory spleens appeared normal grossly. They showed some congestion on microscopic examination and there was much fat in the liver cells. The gastrointestinal tract, gall-bladder, and pancreas were normal. Both adrenals were grossly normal, while microscopically there was an excess of fat in the cortical cells. The uterus was small and the ovaries appeared normal, each containing corpora lutea. Multiple sections of the brain disclosed no abnormality.

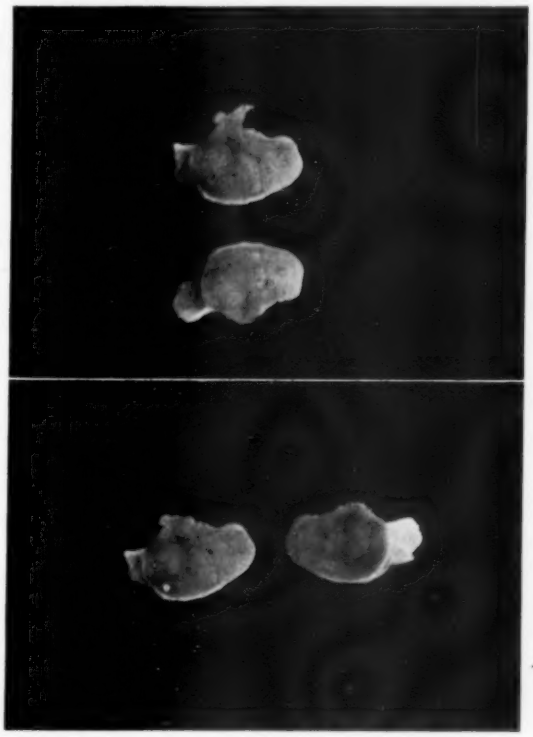

FIG. 3. Top photograph showing a lateral view of the pituitary after removal from the sella. The flattened lateral surfaces are well shown.
Bottom photograph shows the cut surface of the pituitary after sagittal section.

DISCUSSION

It seems reasonable to suppose that the anatomical defect of the hypophysis antedated the nephritis, since there was no evidence of recent change in the position of the internal carotid arteries. Search of the recent literature has not produced any mention of similar defects.* If this anomaly is a rare one, as seems probable, then its presence in a case of nephritis would appear to be merely a coincidence. From the standpoint of clinical diagnosis, the presence of a gross deformity of the pituitary gland which could not be detected by lateral

* In a personal communication to Dr. Rhoads, Dr. Cushing stated that he had never seen an anomaly of this type.

stereoscopic radiograms of the skull seems significant. While it is recognized that roentgen-ray diagnosis of a normal sella turcica does not necessarily exclude gross defects of the hypophysis, nevertheless the anomaly in this case occasioned considerable surprise at the autopsy table.

The basophilic hyperplasia found in the anterior lobe may have been a result of injury by the lateral compression. From their frequent occurrence in the clinical syndrome of pituitary basophilia, it appears that the obesity, glycosuria, and menstrual irregularity were resultant effects of the hyperplasia. The duration of these symptoms would suggest that the basophilic condition was present for some time before the onset of nephritis. The possible causal relationship between pituitary basophilism and renal disease has been discussed fully by Cushing (1932, 1934) and by MacMahon, Close, and Hass (1934). Cushing (1934) states that "It has been pointed out separately by Erdheim, Tolken, Kraus, and Berblinger that an increase of basophilic elements in the glands as a whole is an accompaniment of advancing years of life when naturally enough it is often associated with atherosclerosis and renal disease." Nevertheless there has been a high incidence of nephritis among the cases of basophile adenoma in young adults which have been reported since the clinical syndrome of pituitary basophilism was described by Cushing (1932). In Cushing's original series, five out of eight patients who came to autopsy presented chronic nephritis of some degree. The cases reported by MacMahon, Close, and Hass (1934); Russell, Evans, and Crooke (1935); and Close (1935) all exhibited renal damage in varying amount. Those of Pardee (1934) and Hildebrand (1935) were apparently normal in this respect, although Pardee made little mention of urinary findings. Cushing (1932) suggested that the nephritis in his cases was probably secondary to the hypertension. However, just as in malignant hypertension, there is no *a priori* reason to assume that the nephritis may not come to dominate the picture. In the present case, it is not known whether hypertension antedated the onset of nephritis. Since the pituitary symptoms were present at an earlier date and since the pituitary at autopsy showed no evidence of recent change, it may be supposed with some certainty that the basophilic hyperplasia was present before the nephritis.

The course of the patient's (clinical) condition, and of the renal, blood and circulatory pictures, were quite similar to those observed in typical progressive chronic nephritis, without the pituitary element. The onset was insidious and the disease progressed in a little over two years to a fatal outcome, in accordance with the clinical dictum that gradual onset lends a bad prognosis in hemorrhagic nephritis. Good nutrition was maintained on a high-protein, low-salt diet * until a few weeks before death. Despite the high protein intake, which included supplements of casein up to 30 grams daily, the plasma protein remained low, and the deficit was entirely in the albumin fraction. The excretion of urinary protein averaged about 10 grams daily. The effect of low salt intake showed itself promptly in loss of edema fluid on each admission. Anemia was rather marked, so that the hemoglobin values averaged about 50 per cent of normal during the last five months of illness. Hematuria was never excessive. The blood pressure and cardiac hypertrophy were not unusual for nephritis. Most

* An effort was made to keep the protein intake up to 100 grams daily during the first admission. Because of the patient's capricious appetite, this was not accomplished with any regularity. Salt intake was kept below 1 gram daily.

of the characteristics summarized by Page † (1936) for a typical case of progressive nephritis were present in this patient.

SUMMARY

1. A case of chronic hemorrhagic Bright's disease with clinical features suggestive of pituitary dystrophy is described. The clinical impression of hypophyseal disorder was confirmed by the postmortem finding of a grossly abnormal pituitary gland which contained a preponderance of basophilic elements.

2. The changes in renal function, circulatory system, edema, anemia, etc., were in degree and rate of progress, typical of an actively progressing nephritis. The pituitary anomaly had no obvious effect on the character or course of the nephritic syndrome.

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COMPLETE AURICULOVENTRICULAR DISSOCIATION DUE TO DIGITALIS, WITHOUT SYSTEMIC EFFECTS OF OVERDOSAGE: REPORT OF A CASE*

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THE protean manifestations of digitalis intoxication, which consist of gastrointestinal disturbances, color vision phenomena and digitalis delirium, are well recognized. A group of electrocardiographic changes, including coupled beats, extrasystoles, ectopic rhythm, and conductive defects of varying degrees, is not infrequently encountered. It has long been known that changes in the T-wave (one variety of which is characteristic of digitalis poisoning) occur with great frequency and that they may be noted before any digestive disturbances have

† There was an excess of basophilic elements in the anterior hypophysis in this case also. Page (1936) did not find any clinical signs or symptoms suggestive of pituitary dysfunction in his case, however.

* Submitted for publication May 7, 1937.

occurred. It is doubtful, however, whether it is universally recognized that certain instances of gross overdigitalization, which are characterized by profound electrocardiographic changes, may not be associated with any of the usual systemic effects.

Case Report

A woman, 39 years of age, who was rather high-strung and nervous, came to The Mayo Clinic in June 1936, complaining of palpitation on exertion or excitement. This had been present since she had been a girl. There was no history of rheumatic fever or of hypertension. She had gone through three pregnancies without incident; it had required an unusual amount of exertion to bring on breathlessness. There was no history of dependent edema, nor had she been subject to syncopal seizures. Because of the symptoms referable to her heart, one tablet of digitalis had been administered three times daily for about five weeks before her registration at the clinic and she had continued to take this dose until a few days before her first examination at the clinic.

For 10 years she had been troubled with epigastric bloating and fullness, which had not had any definite quantitative or qualitative relationship to the ingestion of food. During the few weeks prior to her visit to the clinic, these symptoms had, if anything, improved. There had not been any anorexia, nausea, vomiting, or disturbance of the bowels. Physical examination did not reveal any abnormality except an arrhythmia, the nature of which is disclosed by the electrocardiographic studies. The value for the systolic blood pressure was 110 millimeters of mercury and that for the diastolic was 64 millimeters. The pulse rate, when the patient was first seen, was 80 beats per minute. It was noted that pressure on the carotid sinus promptly caused a marked slowing of the pulse rate. There was not any enlargement of the heart or any bruits. The results of laboratory studies, including urinalysis, blood counts, roentgenographic studies of the heart and lungs, gall-bladder, and stomach, were all reported as normal. It was possible to keep the patient under observation for only a matter of 11 days. During this time, electrocardiographic studies, which were repeated on several days (figure 1*a*, *b* and *c*), revealed a gradual transition toward normal. Pressure over the carotid sinus caused very definite bradycardia, but as the digitalis effects wore off, it was no longer possible to elicit this phenomenon.

Comment

The absence of any probable basis for cardiac disease, the nature of the symptoms and their duration, the absence of the usual features associated with complete heart block, and the history of administration of relatively large doses of digitalis led us to suspect the true nature of the trouble. With our present incomplete knowledge of the carotid sinus reflex, we are unable to explain the peculiar electrocardiographic observations noted when pressure is applied over the carotid sinus, but we wish to record them as interesting findings.

It is frequently difficult to gauge the approximate amount of the drug administered in a given period of time from the history, and it is possible that certain patients have a heightened cardiac susceptibility to even small amounts of drugs which belong to the digitalis group. Yet, in the cases in which digitalis is clearly indicated, these changes, except perhaps for diphasic or inverted T-waves in the great majority of cases, fail to occur until clinical effects of overdosage become apparent.

Obviously, if an electrocardiographic record taken prior to the institution of digitalis therapy is not available under these circumstances, these changes

might be erroneously interpreted as indicative of severe myocardial damage, the result of organic heart disease. Moreover, should the patient present either clinical evidence of, or a background which may constitute the basis for, cardiac disease, the seriousness of that disease may be unnecessarily overestimated.

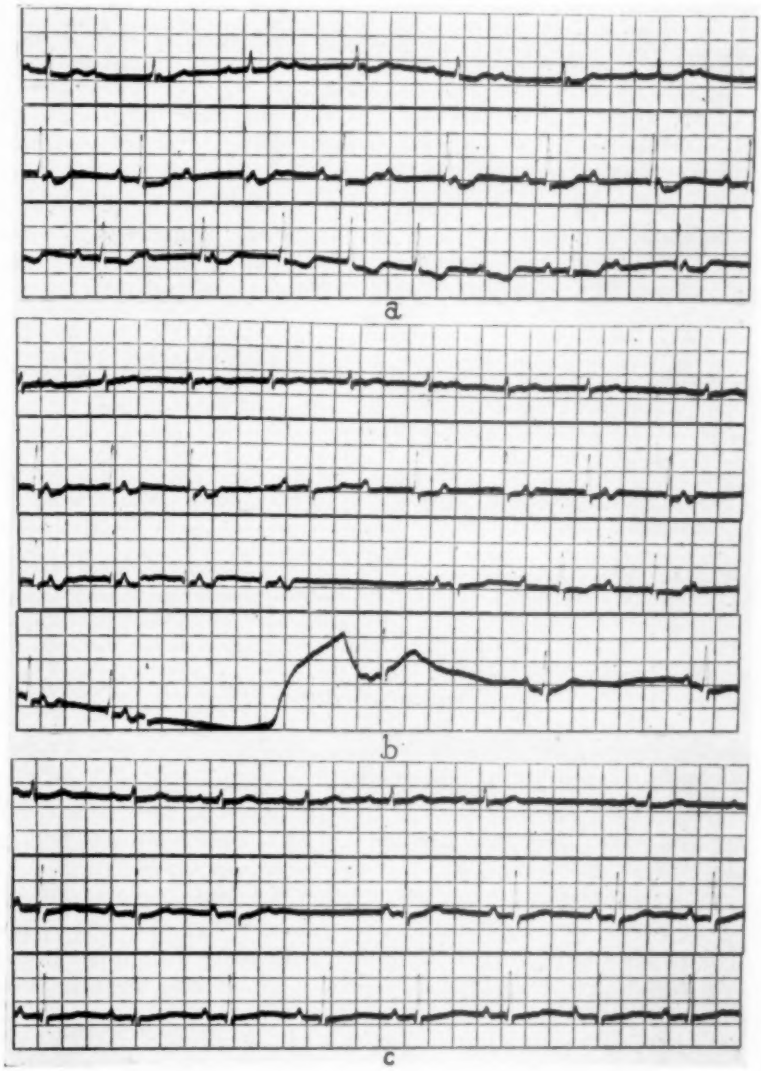

FIG. 1*a*. Electrocardiogram (June 18, 1936) showing complete auriculoventricular dissociation; the auricular rate is 106 and the ventricular rate is 70 per minute; one may note a short series of nodal premature contractions and inversion of the T-waves in Leads II and III; *b*, electrocardiogram (June 22, 1936) showing a rate of 80, nodal rhythm, periods of auriculoventricular dissociation, and a dropped beat; carotid pressure caused definite slowing of the heart; *c*, electrocardiogram (June 25, 1936) showing a rate of 65, sinus rhythm, sinoauricular block with upright T-waves in Leads I and II, and a diphasic T-wave in Lead III.

Errors in diagnosis in these circumstances can be avoided if a sufficiently careful inquiry is made into the cardiac status of the patient prior to the institution of treatment. It is usually possible to ascertain whether there is any reason why organic heart disease might be present, such as the existence or history of hypertension, syphilis or coronary disease, including myocardial vascular accidents. Valvular lesions, both acquired and congenital, can be ascertained or ruled out by physical examination; again, one's suspicions should be aroused when the particular electrocardiographic pattern does not fit the pathologic picture (if any) presented by the patient.

This is well illustrated by the case of a woman, aged 42 years, who had a history of hypertension, but who had reasonably good tolerance to exertion. There was no cardiac enlargement and no history or evidence of congestive heart failure. She never had experienced pain which could in any way be labelled as anginal. The remarks noted at the time the patient was first seen were as follows: "The electrocardiographic changes are out of all proportion to the symptoms in spite of the hypertension." Furthermore, unless this patient had

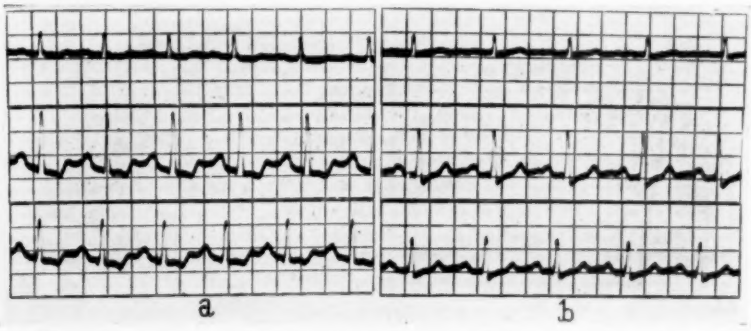

FIG. 2*a*. Sinus rhythm with inversion of T-waves in Leads II and III; *b*, a normal electrocardiogram.

had a previous myocardial infarct in the posterior basal part of the left ventricle (and we were sure that she had not, from the history), if any changes in the T-wave were present as a result of the hypertension, they should have been prominent in Leads I and II. Rheumatic heart disease with right ventricular strain might cause such changes in the electrocardiogram but this could readily be excluded by physical examination. After discontinuing all of her medications, one of which was digitalis, the electrocardiogram reverted completely to normal (figure 2*a* and *b*). It is important to remember also that the effects of digitalis on the electrocardiogram may persist for as long as three weeks after administration of the drug is discontinued.

Digitalis has its clear-cut indications in auricular fibrillation or as an adjunct to quinidine in auricular flutter, in certain cases of congestive heart failure, with or without an ectopic rhythm, and in certain instances in which the episodes of acute ventricular failure characterized by nocturnal dyspnea are not relieved by rest alone. The indiscriminate administration of an otherwise unequalled cardiac remedy for "all that ails" is to be strongly deprecated, particularly in those instances in which a frank discussion and a simple explanation of the mechanism of a variety of functional symptoms referable to the cardiovascular

system will suffice to reassure the patient and to relieve his mind as to any seriousness of their significance. Moreover, if digitalis therapy should be deemed necessary, the physician who prescribes this drug assumes the responsibility not only of administering it in amounts large enough to produce the desired pharmacologic effects, but also in amounts which shall not exceed the limits of physiologic safety.

Summary

A case is reported in which too large a dosage of digitalis caused complete auriculoventricular dissociation. Despite profound electrocardiographic changes, systemic toxic effects were entirely absent. In this particular instance, the symptoms referable to the cardiac system were not the result of organic heart disease, and digitalis, far from being indicated in the management of the condition, might readily have led to confusion in its diagnosis and an unwarranted seriousness in the prognosis.

EDITORIAL

PROTAMINE INSULIN AND DIET IN DIABETES MELLITUS

BEFORE enumerating methods for achieving the best regulation of the diabetic regimen it is important to marshall the available facts that throw light on this phase of the disease. Only in this way can we clarify our objective and estimate the degree of success attained.

Adequate regulation of a patient with diabetes mellitus has been thought for a long time to consist in balancing the diet and insulin in a way that maintains the urine free from sugar, avoids periods of hyperglycemia, and at the same time avoids insulin reactions. In many patients this degree of regulation has not been possible and the ones who are difficult to regulate often vacillate precipitously from insulin shock to diabetic coma. With the use of protamine zinc insulin smooth adjustment occasionally is even more difficult and some of the more critical physicians who are especially interested in diabetes mellitus say that they have never seen a patient " regulated " on one daily dose of protamine insulin.

Some specialists in the treatment of diabetes advocate a high carbohydrate diet with one morning dose of protamine insulin which, in severe cases, may or may not be augmented by a simultaneous dose of regular insulin and they more or less ignore the presence of sugar in the urine up to as much as 40 gm. in 24 hours. It is obvious that such a regimen includes not only glycosuria but periods of marked hyperglycemia. Mosenthal [1] in 1935 expressed the belief that the damage done to the patient with diabetes mellitus occurred not from the abnormally high level of blood sugar but rather from the long continued effects of glycosuria with its attendant polyuria. In considering Mosenthal's hypothesis we can say in the first place that patients with renal glycosuria [2] may excrete large quantities of sugar in the urine over periods of years without any evidence of damage resulting therefrom except undernutrition. This fact justifies some doubt as to the correctness of Mosenthal's principle. There is still the possibility that polyuria in a patient with true diabetes is more serious than in one with merely a low renal threshold for glucose but convincing evidence is lacking. In the second place there is fresh evidence to suggest that a patient whose urine is sugar free and whose blood sugar is constantly within normal limits may still not be properly regulated if the depots of glycogen, particularly in the liver, are not maintained at a normal level. It is clearly shown by de Wesselow and Griffiths [3] that it is impossible to classify patients as permanently insulin sensitive or insulin resistant. Patients who are insulin resistant become sensitive to insulin by carefully balancing a high carbohydrate intake

[1] MOSENTHAL, H. O.: Hyperglycemia; evaluation in treatment of diabetes mellitus, Jr. Am. Med. Assoc., 1935, cv, 484–488.

[2] THOMAS, H. M., JR.: The renal threshold for glucose, ANN. INT. MED. (In press.)

[3] DE WESSELOW, O. L. V., and GRIFFITHS, W. J.: Insulin resistance in diabetes mellitus and the effect of dietary carbohydrate, Quart. Jr. Med., N. S., 1938, vii, 17–28.

with adequate doses of insulin. Bridge [4] has come to the same conclusions from his studies on the action of insulin on glycogen reserves. He found in rabbits that large doses of insulin given during the course of glucose infusion serve to deposit more glycogen in the muscle and less in the liver but do not result in increasing the respiratory quotient. He has also found that after a poorly regulated patient with diabetes mellitus has been on a controlled high carbohydrate regimen for some time the respiratory quotient does become higher.[5] Bridge, like de Wesselow and Griffiths, believes that this is brought about by an increase in the amount of hepatic glycogen and an improvement of glycogen metabolism in the liver. These findings are in accord with the statements of many clinicians that their patients are very much better while on a high carbohydrate diet.

It is impossible to say at present whether hyperglycemia and glycosuria are harmful if in other respects the sugar metabolism in the body is essentially normal. We can say, on the other hand, that severe insulin shocks and possibly repeated mild attacks of hypoglycemia are harmful and in the face of arteriosclerotic coronary or cerebral arteries are actually dangerous.

For the past decade several clinics both abroad and in this country have prescribed very high carbohydrate diets amounting to 300 or 400 gm. of carbohydrate a day. Most clinics refuse to be quite so radical but practically all have been influenced to a greater or less extent. The general experience with diets containing between 150 and 225 gm. of carbohydrates a day is that the patient feels better, likes his food better, needs little or no more insulin than on a lower diet and has fewer insulin reactions. It is interesting to find a rational explanation of these beneficial results in an improved hepatic glycogen metabolism with coincidental improvement in insulin utilization.

Protamine insulin introduces new problems of regulation. Since the absorption rate is so much slower than regular insulin the full effect from an injection is not obtained for five or six hours. After that the effect is more or less constant for the next 18 or 20 hours although the injected insulin is more rapidly utilized if food is taken than when it is not. Hypoglycemic reactions are usually encountered in the early morning hours after the long period of fasting during sleep. These facts necessitate certain changes in the dietary regime. Since the rate of absorption of protamine insulin is thought to be more uniform than the rate of production of endogenous insulin of a normal individual it is well to supply the carbohydrate in somewhat smaller amounts at shorter intervals. The indications may be met by starting the day with a small carbohydrate meal and by supplying some carbohydrate just before retiring at night. Another satisfactory formula for distributing the carbohydrate during the 24 hours is to divide

[4] Bridge, E. M.: The action of insulin on glycogen reserve, Bull. Johns Hopkins Hosp., 1938, lxii, 408–421.

[5] Bridge, E. M., and Winter, E. A.: Diabetes, carbohydrate combustion and insulin action, Bull. Johns Hopkins Hosp. (In press.)

the total amount into ⅕, ⅖, ⅖, for the three meals and then to subtract 10 gm. from each meal and present it in a convenient form three hours after meals.

If, then, one subscribes to the principle that the diet must contain enough carbohydrate to keep the hepatic storehouse of glycogen at a high level it is logical to place the lowest limit of carbohydrate in the diet at 150 gm. a day. If the patient's caloric requirement permits, this amount may be increased to 200 gm. or 225 gm. daily. It is customary to keep the protein at the lowest level which is consistent with nitrogen balance and the fat low enough to prevent the patient from gaining weight or, if already overweight, to bring about a gradual loss of weight. Blood sugar estimations at intervals during the day and night often show normal variations when suitable protamine insulin dosage is given.

Unusual exercise is frequently followed by hypoglycemia. However, patients become familiar with this consequence of unusual exertion and learn to forestall severe attacks by eating extra bread or fruit or some other readily available carbohydrate. Where an amount of exercise customary to the patient is followed by a hypoglycemic reaction, reduction of the protamine insulin dosage is indicated but after the reduction glycosuria must be watched for more carefully than before.

Moderate variations in blood sugar levels are unimportant and extreme ones make themselves evident to the watchful patient in a way that enables him to change his single dose of insulin or his diet to suit the situation. It has been shown that excellent regulation with protamine insulin can be obtained by proper dietary adjustment of an adequately high carbohydrate intake. The patient not only is happier and feels very much better on this than on any other regimen but also the metabolic processes more nearly approach normal.

H. M. T., Jr.

REVIEWS

Protoformotherapy in Treatment and Prevention. By N. E. ISCHLONDSKY. 237 pages; 15 × 26 cm. H. Kimpton, London. 1937. Price, $5.00.

The author has combined a series of lectures delivered before the Egyptian Medical Association of the University of Cairo into the above volume. "Protoformotherapy," as defined, "is a basic conception, the most characteristic feature of which is the widest application of synthesis in the interpretation of morbid phenomena." The idea is based upon the supposed stimulation of the natural protective capacities of the organism by injection of an incret derived from embryos during the third and fourth month of gestation. The incret is advocated by the author for the treatment of innumerable disease states; pulmonary tuberculosis, chronic nephritis, endocrine disturbances and epileptiform states, constitute only a small number. In support of the extraordinary results obtained in the treatment of these conditions, the author offers extremely inadequate case reports. An inadequacy which in view of the monumental claims made by the author, throws great doubt upon the value of the work.

J. E. B.

In the Realm of Mind. By CHARLES S. MYERS, Psychologist. 251 pages; 12 × 18 cm. Cambridge University Press, London; Macmillan Co., New York. 1938. Price, $2.50.

This book is made up of nine chapters on the applications and implications of psychology in the relationships of human society. The fourth chapter will be of especial interest to medical readers as it is entitled "A Psychological Regard of Medical Education," and is a reprint of the Bradshaw Lecture, delivered before the Royal College of Physicians.

The author feels that our present system of medical education tends to turn out specialists rather than clinicians, because medical education is "almost wholly in the possession of specialists, each with his own vested interests, each maintaining the supreme importance of a full knowledge of his subject for the medical student, and strenuously opposing any reduction in the time devoted to it." He makes a plea that the future clinician should receive first a more general education in the whole range of medicine and surgery before he visits the "too water-tight departments of the specialist physicians and surgeons expressly to learn about the rarer diseases—but specialization should follow, not form part of, elementary medical education."

In the other chapters of this book the reader will find many thought provoking statements, and no doubt will agree with the author that "psychology unquestionably offers great help in the choice of a career."

J. L. McC.

A Diabetic Manual. By EDWARD L. BORTZ, M.D. 222 pages; 14 × 20.5 cm. F. A. Davis Co., Philadelphia. 1936.

Five authors have contributed to Dr. Bortz's Manual for Diabetics. There is an interesting foreword by Dr. George Morris Piersol. There is already a considerable number of manuals for diabetics available, but the present one presents many good features. It is very readable and many of the sections are outstanding; for example those upon the "Administration of Insulin" and the "Care of the Feet." The chapter given up to the associated condition, obesity, is interesting and instructive.

It appears as if the use and dangers of protamine-zinc-insulin were not given adequate discussion. It is questionable whether it is justifiable to say that "certain . . . cases of renal glycosuria develop a mild form of diabetes in later years." There is some question also whether certain parts of the manual are not more suited for the comprehension of physicians than for that of patients.

J. S. E.

A Textbook of Medicine. Edited by RUSSELL L. CECIL, A.B., M.D., Sc.D.; Associate Editor for Diseases of the Nervous System, FOSTER KENNEDY, M.D., F.R.S.E. Fourth Edition, revised. 1614 pages; 17 × 25 cm. W. B. Saunders Co., Philadelphia. 1937. Price, $9.00.

There can be no doubt that the new edition of this text will establish even more firmly its rapidly growing popularity. One hundred and forty authors have contributed to it, and the reader cannot but be impressed by the excellent editing and arrangement of the work—a difficult undertaking with such a large number of writers. The style is uniformly clear and concise and at the same time very readable and interesting.

Nine additional subjects have been introduced to the present volume. Twenty-nine subjects have been rewritten by authors new to the Textbook, partly because of the death of some of the former contributors, and partly because of a new editorial policy of retiring older writers and replacing their work by that of a younger group of teachers. The Editor, in his preface, regrets the loss of some of the articles, but his good judgment in selecting new contributors has made the present edition one of the best textbooks available, both for the student and practitioner.

T. N. C.

COLLEGE NEWS NOTES

Gifts to the College Library

Grateful acknowledgment is made of the receipt of the following donations to the College Library:

Books

Dr. F. M. Pottenger (Fellow and Regent), Monrovia, Calif.—an autographed copy, Fifth Edition, "Symptoms of Visceral Disease";
Dr. Emanuel M. Josephson, New York, N. Y.—"Glaucoma and Its Medical Treatment with Cortin."

Reprints

Dr. George E. Baker (Associate), Casper, Wyo.—3 reprints;
Dr. Karl F. Eschelman (Fellow), Buffalo, N. Y.—1 reprint;
Dr. James O. Finney (Associate), Gadsden, Ala.—3 reprints;
Dr. William Freeman (Fellow), Worcester, Mass.—1 reprint;
Dr. Hyman I. Goldstein (Associate), Camden, N. J.—2 reprints;
Dr. Irving Gray (Fellow), Brooklyn, N. Y.—26 reprints;
Dr. Jacob Gutman (Fellow), Brooklyn, N. Y.—Second Series Supplement to "The Modern Drug Encyclopedia";
Dr. J. Morrison Hutcheson (Fellow and Governor for Virginia), Richmond, Va.—1 reprint;
Dr. Vincent W. Koch (Fellow), Janesville, Wis.—1 reprint;
Dr. Manfred Kraemer (Fellow), Newark, N. J.—2 reprints;
Dr. Charles E. Lyght (Associate), Northfield, Minn.—4 reprints;
Dr. Arthur M. Master (Fellow), New York, N. Y.—20 reprints;
Dr. William B. Rawls (Fellow), New York, N. Y.—1 reprint;
Dr. David Salkin (Associate), Hopemont, W. Va.—1 reprint;
Dr. Benjamin Saslow (Associate), Newark, N. J.—1 reprint;
Dr. Jacob Schwartz (Associate), Brooklyn, N. Y.—1 reprint;
Dr. Christopher C. Shaw (Associate), Bellows Falls, Vt.—7 reprints;
Dr. Frederick R. Taylor (Fellow), High Point, N. C.—Chapter VI-B and Chapter XIV-E, Oxford Loose-Leaf Medicine;
Dr. Edward G. Thorp (Fellow), Boston, Mass.—5 reprints;
Dr. Walter H. Watterson (Fellow), La Grange, Ill.—1 reprint;
Dr. Samuel Weiss (Fellow), New York, N. Y.—3 reprints.

Dr. M. C. Pincoffs (Fellow), Baltimore, Md., contributed a reprint by Dr. Lewellys F. Barker (Fellow), Baltimore, Md., on "Comments on Tetany," the original article appearing in Volume I, No. 4, February, 1921, of the "Annals of Medicine," the original official publication of the College.

New Life Members

Dr. Emanuel Klaus (Fellow), Cleveland, Ohio, and Dr. Harry W. Coffin (Fellow), Los Angeles, Calif., have become Life Members of the American College of Physicians, making a total of one hundred and one members who have subscribed to Life Membership, four of whom are now deceased.

Maryland Chapter of the College

On April 19 Fellows of the College residing in Maryland held a meeting under the chairmanship of Dr. Henry M. Thomas, Jr. (Fellow and Governor of the College for Maryland), at which it was decided to establish a so-called Maryland Chapter of the members of the College. Dr. Sydney R. Miller (Fellow), Baltimore, was elected chairman for the first year. It is planned to have at least two meetings a year and other meetings if special circumstances arise.

Through arrangements by the American Heart Association, New York City, leading British and American physicians, 6,000 miles apart, conferred via the radio on Rheumatic Heart Disease, the greatest menace to child health. This conference, the first international broadcast on any health problem, was heard over the National Broadcasting Company, WEAF and the Red Network, on May 2, in connection with the observance of National Child Health Day. The conference was opened by Lord Thomas Jeeves Horder, Physician-in-ordinary to the King of England, from London. Dr. Homer F. Swift of the Rockefeller Institute, New York City, and Dr. T. Duckett Jones of the House of the Good Samaritan, Boston, spoke from Atlantic City, where they were attending the convention of the American Society for Clinical Investigation. Dr. William J. Kerr, President of the American College of Physicians and of the American Heart Association, took up the discussion from San Francisco.

Under the Presidency of Dr. Alphonse McMahon (Fellow), St. Louis, the American Therapeutic Society held its Thirty-Ninth Annual Meeting at the Waldorf-Astoria Hotel in New York City, April 1–2, 1938. Among its officers were Dr. Harold S. Davidson (Fellow), Atlantic City, and Dr. Hal McCluney Davison (Fellow), Atlanta, Ga., Vice Presidents; Dr. Oscar B. Hunter (Fellow), Washington, D. C., Secretary; Dr. Henry H. Turner (Fellow), Oklahoma City, Treasurer. On its Council of fifteen members all but four are Fellows of the College. All but a very few of the Fellows and Active Members of this Society are Fellows of the College. The majority of those presenting papers at the New York meeting were also Fellows of the College. Dr. F. M. Pottenger (Fellow and Regent), Monrovia, Calif., was a speaker of the evening at the annual dinner and President's Reception. Dr. Reynold Webb Wilcox, deceased, first president of the American College of Physicians, was the second president of the American Therapeutic Society.

Dr. William G. Herrman Receives Rutgers Award

Dr. William G. Herrman (Fellow), Asbury Park, N. J., was the recipient of the Rutgers' Award, a medal of honor by Rutgers University for his outstanding service to society in the field of medicine, and for his loyalty to his Alma Mater, from which he graduated in 1912. The presentation was made on February 22, 1938, at a dinner celebrating the annual Alumni Day by the College. The medal was presented by Dr. Robert Clothier, President of the University.

Citation

" Here, in the presence of your fellow-alumni, I want to pay the University's tribute to you for your services, both to your University and to your profession. Voltaire wrote: ' But nothing is more estimable than a physician who, having studied nature from his very youth, knows the properties of the human body,

the diseases which assail it, the remedies which will benefit it, exercises his art with caution and pays equal attention to the rich and poor.' In war and in peace, you have practiced your profession with achievement and with promise of yet greater achievement to come, especially with reference to the application of radiology and roentgenology to medicine. In recognition of your attainments, you have been made a Fellow of the American College of Physicians and of the American College of Radiology—and only recently the President of the Medical Society of New Jersey.

"Yet, despite the exacting demands of your professional work, you have always found time to wear a trail back to the campus where you studied in those years prior to 1912. Your counsel and support have always been available to your Alma Mater. It is appropriate that, with the authority of the Trustees, I should confer on you today the Rutgers University Award. This medal, which I hand you, is the visible token of our tribute."

Dr. Hilton S. Read (Fellow), Atlantic City, is the chairman of the Welfare Committee (executive body) of the Medical Society of New Jersey.

The Desert Sanatorium of Southern Arizona, located at Tucson, is conducting a special program and special low rates for arthritics from May 15 to October 15, 1938. The Sanatorium does not stress nor exploit any particular method of treatment of arthritis, but, following out good medical practice, bases therapy upon the diagnostic findings in each case.

Dr. Roland Davison (Fellow) is the Medical Director and Dr. C. W. Mills (Fellow) is the Chief Visiting Physician.

Dr. Joseph Hajek (Fellow) and Dr. Thomas T. Mackie (Fellow), both of New York City, were Chairman and Secretary, respectively, of the Section on Medicine of the New York Academy of Medicine for the year 1937–38.

Dr. Hajek contributed a paper on "The Cardiogram in Health and Disease" on the Scientific Program of the South Brooklyn Medical Society Meeting, April 14, 1938.

Dr. Ross M. Lymburner (Fellow), Hamilton, Ontario, spoke on "The Treatment and Later Management of Coronary Thrombosis" before the annual meeting of the Ontario Medical Association, held at the Royal York Hotel, Toronto, Ontario, May 2 to 6.

Dr. H. I. Spector (Associate), St. Louis, has received a joint invitation from the Kansas State Medical Society, Kansas State Board of Health and the Kansas Tuberculosis and Health Association to lecture to the medical societies of several cities of the State of Kansas on the subject of "Symptoms, Diagnosis and Differential Diagnosis of Early Pulmonary Tuberculosis." He was the guest of the Leavenworth County Medical Society on April 18, of the Franklin County Medical Society in Ottawa on April 19, of the Sedgwick County Medical Society in Wichita on April 21, and of the Central Kansas Medical Society in Russell on April 22.

On March 10, 1938, the Morgan County (Illinois) Medical Society held its Fiftieth Anniversary Celebration Meeting, honoring Dr. Frank Parsons Norbury (Fellow), of Jacksonville, Ill. The speakers included Hon. A. L. Bowen, Director of the Department of Public Welfare, State of Illinois; Dr. Tom B. Throckmorton (Fellow), Des Moines, Iowa; and Dr. Charles L. Patton, F.A.C.S., Springfield, Ill.

On February 8, 1938, members of the American College of Physicians in Puerto Rico gave a farewell dinner to Dr. Ramón M. Suárez, Governor of the College for Puerto Rico, preceding his sailing to participate in the postgraduate course offered under the auspices of the College at Harvard University. Among the Puerto Rico members present were Dr. Ramón M. Suárez, Dr. Carlos E. Muñoz MacCormick, Dr. Guillermo Marqués, Dr. Antonio Ortiz, Dr. Luis Morales, Dr. César Domínguez, Dr. R. Rodríguez-Molina, Dr. Enrique Koppisch, Dr. José Landrón, Dr. O. Costa-Mandry and Dr. José Garrido Collazo.

Dr. Suárez later attended the Annual Session of the College at New York City, taking his place on the Board of Governors as the representative from Puerto Rico. On behalf of the Fellows and Associates of the College in Puerto Rico, Dr. Suárez presented a set of resolutions signed by all the Puerto Rico members, inviting the College to come to Puerto Rico on a post-convention cruise to inspect their work and institutions.

Dr. Warren F. Kahle (Fellow), 17 N. Chatsworth Avenue, Larchmont, N. Y., has prepared a very interesting and instructive talking slide film on the subject, "Treating Pneumonia." This film has but recently been completed, and Dr. Kahle has expressed his willingness to loan it to Fellows of the College. It requires twenty-three minutes, and is a combination of still and talking film. The apparatus for showing the film is available in practically every community. The film and the record may be loaned, or Dr. Kahle will show it personally to groups not too far removed from Larchmont.

The Chicago Tumor Institute opened March 21, 1938, offering consultation service to physicians in the diagnosis and treatment of cancer and radiation facilities for cancer patients. The Institute also proposes to conduct research and to offer training to physicians who may wish to qualify as specialists in the study and treatment of this disease. The scientific committee consists of Max Cutler, M.D., Director; Sir G. Lenthal Cheatle, F.R.C.S.; Henri Coutard, M.D.; Arthur H. Compton, Ph.D.; and Ludvig Hektoen, M.D.

Dr. A. A. Leonidoff (Associate), Poughkeepsie, N. Y., addressed the Dutchess County Psychiatrical Society March 18, 1938, on "Control of Tuberculosis in the Hudson River State Hospital."

Dr. Arthur J. Logie (Associate), Jacksonville, Fla., addressed the Polk County Medical Society at Lakeland, Fla., on January 12, 1938; the Suwannee River Medical Society at Mayo, Fla., on February 11, 1938; the Florida Tuberculosis Association at Orlando, Fla., on April 26, 1938; and the Duval County Medical Society at Jacksonville, Fla., on May 2, 1938. His subject was "The Value and Significance of the Tuberculin Test."

Dr. M. Coleman Harris (Fellow), New York City, has been advanced to Adjunct Professor of Medicine and Head of the Department of Allergy at the New York Polyclinic Hospital. Because of the added duties of this new appointment, he has resigned his appointment at Roosevelt Hospital.

Under the presidency of Dr. Edward S. Sledge (Fellow), Mobile, the Medical Association of the State of Alabama held its annual meeting in Mobile, April 19–21. Among members of the College who contributed to the program were Dr. John H. Musser (Fellow), New Orleans, "Treatment of Organic and Inorganic Diseases of the Stomach"; Dr. Oscar W. Bethea (Fellow), New Orleans, "The Pneumonias"; and Dr. Joe H. Little (Associate), Mobile, "Progress in the Treatment of Diabetes."

Dr. Thomas M. McMillan (Fellow), Philadelphia, delivered the Jerome Cochran Lecture on "An Optimistic View of Some Problems of Heart Disease."

Dr. Joseph Yampolsky (Fellow), Atlanta, Ga., addressed the Thirteenth Annual Session of the Alabama Pediatric Society, April 18, on "A Comparative Review of the Drugs Used in the Treatment of Syphilis."

Dr. Elliott P. Joslin (Fellow), Boston, addressed the Chicago Medical Society April 6 on "Present Conceptions of Diabetes Mellitus."

Dr. Alan Brown (Fellow), Toronto, Ont., addressed the Northern Tri-State Medical Association in Findlay, Ohio, April 12, on "Some Common Disturbances in Children Frequently Handled Incorrectly."

Dr. M. Herbert Barker (Associate), Chicago, addressed the Arkansas Medical Society at Texarkana April 18–20 on "Phases of Renal Edema and Their Treatment."

Dr. Benjamin W. Black (Fellow), Oakland, and Dr. Clifford W. Mack (Fellow), Livermore, have been appointed to a committee to aid the California State interim committee on state hospitals, authorized by the legislature to study hospitalization of the insane.

Dr. Logan Clendening (Fellow), Kansas City, Mo., delivered a public lecture on "The Care and Feeding of Humans" under the auspices of the Chicago Medical Society at the Goodman Theater in Chicago on April 13.

Dr. William Devitt (Fellow), Allenwood, Pa., was elected president of the Pennsylvania Tuberculosis Society.

Dr. Udo J. Wile (Fellow), Ann Arbor, addressed the Allegheny County (Pa.) Medical Society at Pittsburgh, April 19, on "Syphilis in Relation to Surgical Problems."

Dr. John Zahorsky (Fellow), St. Louis, addressed the one hundred and fifth annual meeting of the Tennessee State Medical Association at Nashville, April 12–14, on "The Newborn Baby in the Hospital."

Among guest speakers at the annual meeting of the Texas Tuberculosis Association held in El Paso, April 15–16, were Dr. Jay Arthur Myers (Fellow), Minneapolis, president of the National Tuberculosis Association, and Dr. Lewis J. Moorman (Fellow), Oklahoma City.

Dr. James N. Williams (Associate), Richmond, Va., addressed the sixty-second annual meeting of the American Association on Mental Deficiency at Richmond, April 20–23, on "Emotional Education of Children."

Stanford University School of Medicine, San Francisco, has inaugurated a course of popular medical lectures. Among Fellows of the College who have recently contributed are Dr. Walter W. Boardman (Fellow), San Francisco, "Conditions of the Mouth in Relation to Disease"; Dr. William J. Kerr (Fellow and President), San Francisco, "Forty, Fat and Florid and Heading for Circulatory Failure"; and Dr. Dwight L. Wilbur (Fellow), San Francisco, "Vitamin Facts and Fallacies."

Dr. James S. McLester (Fellow), Birmingham, Ala., delivered the Ewing Fox Howard Oration on "Causes and Effects of Hypertension" before the seventy-first annual session of the Mississippi State Medical Association at Jackson, Miss., April 19–21.

Under the presidency of Dr. Homer Davis (Fellow), Genoa, Nebr., the Nebraska State Medical Association held its annual convention at Lincoln, April 26–28.

Dr. Arthur C. Christie (Fellow), Washington, D. C., delivered the annual J. Chalmers DaCosta Foundation Lecture on "Comprehensive Planning for Medical Care—the Physician's Responsibility," March 30, before the third annual Postgraduate Institute of the Philadelphia County Medical Society. Dr. Rufus S. Reeves (Fellow), Philadelphia, was chairman of the committee that organized the Institute.

Dr. Bernard L. Wyatt (Fellow), Tucson, Ariz., was recently awarded a medal from the Comité National de Défense contre la Tuberculose in France in appreciation of his work in tuberculosis during the World War.

Dr. Robert A. Hare (Fellow), Santa Barbara, Calif., was recently appointed Medical Director of the Washington Sanatorium and Hospital, Takoma Park, Washington, D. C.

Dr. Thomas Parran (Fellow), Surgeon General of the U. S. Public Health Service, was recently awarded a medal by the "Parents Magazine" for outstanding service to children.

Dr. Cyrus C. Sturgis (Fellow), Ann Arbor, addressed the eighty-seventh annual session of the Iowa State Medical Society at Des Moines, May 11–13, on "Diseases Associated with Changes in the Red Blood Cells."

Dr. Ray M. Balyeat (Fellow), Oklahoma City, addressed the Louisiana State Medical Society at New Orleans, May 2–4, on "Common Allergic Manifestations Encountered by the General Practitioner."

Dr. Leonard G. Rowntree (Fellow), Director of the Philadelphia Institute for Medical Research, was the recipient of the annual Strittmatter Award, a gold medal, at a meeting of the Philadelphia County Medical Society on April 13, the award being made in recognition of Dr. Rowntree's work on the thymus gland, cancer and arthritis.

Dr. Eugene F. DuBois (Fellow) and James D. Hardy, New York, addressed the National Academy of Sciences at Washington, D. C., recently on "Relationship of Humidity to Evaporation of Sweat."

Dr. William R. Houston (Fellow), Austin, Texas, was the banquet speaker at the forty-first annual meeting of the American Gastro-Enterological Association at Atlantic City, May 2–3, his subject being, "Our Relations with the Orient." Dr. Houston also addressed the Medical Society of the District of Columbia at the public meeting in connection with its annual scientific assembly May 4–5 on "Western Medicine in China."

Dr. Edward A. Strecker (Fellow), Philadelphia, addressed the one hundred and thirty-second annual meeting of the Medical Society of the State of New York, held in New York City, May 9–12, on "The Importance of Psychology in the Practice of Medicine."

Dr. Paul A. O'Leary (Fellow), Rochester, Minn., addressed one of the sections on "Significance of Asymptomatic Neurosyphilis."

The eighty-fifth annual session of the Medical Society of the State of North Carolina was held at Pinehurst May 2–4, under the presidency of Dr. Wingate M. Johnson (Fellow), Winston-Salem.

Among the guest speakers was Dr. Edward A. Strecker (Fellow), Philadelphia, "Functional Illness and the Medical Psychology Needed by the Practitioner in Its Treatment."

A memorial tablet to the late Dr. William Duffield Robinson (Fellow), was unveiled by the trustees of the Philadelphia Institute for Medical Research at its building at the Philadelphia General Hospital on April 7. Dr. Robinson was active in the formation of the Institute. He died in 1931.

Dr. James B. Collip (Fellow), Montreal, Que., addressed the Philadelphia Pediatric Society April 12 on "Anterior Pituitary Hormones."

Dr. John A. Kolmer (Fellow), Philadelphia, addressed the seventy-second annual session of the Texas State Medical Association at Galveston, May 10–12, on "Syphilis."

The Congress of American Physicians and Surgeons held its Semi-Centenary Meeting at Atlantic City, May 3–4, 1938, under the presidency of Dr. James B. Herrick (Fellow and 1st Vice President), Chicago. The Congress is held every five years. The component associations and societies include the American Otological Society, American Neurological Association, American Gynecological Society*, American Dermatological Association*, American Laryngological Association, American Surgical Association, American Clinical and Climatological Association, Association of American Physicians, American Association of Genito-Urinary Surgeons, American Orthopedic Association, American Pediatric Society*, American Association of Pathologists and Bacteriologists. However, those societies marked with an asterisk did not hold meetings with the Congress this year.

Among the officers of the Association of American Physicians were Dr. George R. Minot (Fellow), Boston, President; Dr. Eugene F. DuBois (Fellow), New York, Vice President; Dr. Hugh J. Morgan (Fellow), Nashville, Tenn., Secretary; Dr. William S. McCann (Fellow), Rochester, N. Y., Treasurer; Dr. Francis G. Blake (Fellow and Governor), New Haven, Conn., Recorder; Dr. Gerald B. Webb (Fellow), Colorado Springs, Dr. Louis Hamman (Fellow), Baltimore, Dr. James H. Means (Fellow and Ex-President), Boston, Dr. George Blumer (Fellow), New Haven, Conn., and Dr. Warfield T. Longcope (Fellow), Baltimore, Members of the Council; Dr. O. H. Perry Pepper (Fellow and President-Elect), Philadelphia, Delegate to the Executive Committee of the Congress; Dr. Ernest E. Irons (Fellow), Chicago, Alternate Delegate; Dr. Richard A. Kern (Fellow), Philadelphia, Alternate Committeeman.

Among the officers of the American Clinical and Climatological Association were Drs. John H. Musser (Fellow), New Orleans, and James J. Waring (Fellow), Denver, Vice Presidents; Dr. Francis M. Rackemann (Fellow), Boston, Secretary and Treasurer; Drs. J. Burns Amberson, Jr. (Fellow), New York, O. H. Perry Pepper (Fellow), Philadelphia, Henry M. Thomas (Fellow and Governor), Baltimore, James E. Paullin (Fellow), Atlanta, and Chester S. Keefer (Fellow), Boston, Members of the Council; Dr. George Morris Piersol (Fellow), Philadelphia, Alternate Delegate to the Executive Committee of the Congress; Dr. Richard A. Kern (Fellow), Philadelphia, member of the Committee on Arrangements.

Among the officers of the American Association of Pathologists and Bacteriologists were Dr. Earl B. McKinley (Fellow), Washington, D. C., Vice President; Dr. Howard T. Karsner (Fellow), Cleveland, Ohio, Secretary; Dr. C. V. Weller (Fellow), Ann Arbor, Member of the Council; Lt. Col. George R. Callander (Fellow), M.C., U. S. A., Delegate to the Executive Committee of the Congress; Dr. Ward J. MacNeal (Fellow), New York, Alternate Delegate.

Dr. Elmer L. Sevringhaus (Fellow), Madison, Wis., was a guest speaker at the ninety-eighth annual meeting of the Illinois State Medical Society at Springfield, May 17–19, his subject being "Pituitary Therapy in General Practice."

Among the guest speakers at the one hundred and forty-seventh annual meeting of the New Hampshire Medical Society at Manchester May 17–18 were Dr. Walter

Bauer (Fellow), Boston, "Treatment of Arthritis"; Dr. Donald S. King (Fellow), Boston, "Cancer of the Lung"; and Dr. Frederick T. Lord (Fellow), Boston, "Treatment of Pneumonia."

Among the guest speakers at the annual meeting of the Medical Society of New Jersey, held at Atlantic City, May 17–19, were Dr. Josephine B. Neal (Fellow), New York, "Treatment of Infections of the Central Nervous System with Special Reference to Sulfanilamide"; and Dr. George B. Eusterman (Fellow), Rochester, Minn., "Newer Aspects in Etiology and Treatment of Ulcers of the Gastrointestinal Tract."

Dr. William S. Rude (Fellow), Ridgetop, was elected a vice-president of the Tennessee State Medical Association at its annual meeting in Nashville during April.

OBITUARIES

DR. LEWIS BURGIN McBRAYER

Lewis Burgin McBrayer died at his home in Southern Pines, N. C., April 1, 1938. He was born in Buncombe County, December 27, 1868, and his long and useful career in medicine from the time of his graduation from the Louisville (Ky.) Medical College in 1889 was spent within the confines of his native State. For twenty-five years he practiced in Asheville, serving as County Coroner of Buncombe County, and City Health Officer of Asheville, becoming, in 1914, the Superintendent of the North Carolina State Tuberculosis Sanatorium, at Sanatorium, N. C.

He was President of the Buncombe County Medical Society about 1900. From 1915 to 1920 he was Secretary of the Hoke County Medical Society; in 1918–19, he was Chairman of the Section on Public Health of the Southern Medical Association; in 1919 he was President of the Moore County Medical Society; in 1925–26 he was President of the Southern Conference on Tuberculosis; he was Managing Director of the North Carolina Tuberculosis Association, and President of the North Carolina Medical Society, as well as a member and President one year of the State Board of Medical Examiners, after which he became Secretary-Treasurer of the State Medical Society, and from 1921 until his retirement two years ago, he was given the title of " Honorary Secretary for Life " of this Society.

Being keenly interested in the furtherance of organized medicine, he was always vitally interested in, and a member of, his local County Medical Society, State Medical Society, the Southern Medical Association, the American Medical Association, the National Tuberculosis Association and its regional subdivisions, and the American College of Physicians, of which he became a Fellow in 1920, maintaining an active interest in all of these associations until illness incapacitated him.

In 1890, Dr. McBrayer married Miss Lillian Cordie Deaver, of Asheville, of which union three children survive: Mrs. Paul P. McCain, wife of Paul P. McCain, M.D., F.A.C.P., present Superintendent of the North Carolina State Tuberculosis Sanatorium; Lewis B. McBrayer, Jr., and Reuben A. McBrayer.

Dr. McBrayer was actively interested in the Order of Odd Fellows, which organization gave him some of its highest honors, he finally serving in 1933–34 as Grand Marshal of the sovereign grand lodge. His civic interests embraced the Sand Hill Fruit Growers Association, of which he was President in 1922; the Chamber of Commerce of Southern Pines; the United States No. 1 Highway Association, both of which latter organizations he also served as President. Dr. McBrayer's outstanding contribution to the medical life of his State was his vitalizing interest and campaigns for the betterment of public health, and for the prevention and eradication of

tuberculosis. In the American College of Physicians, he was so far as known the initiator of the idea of sectional meetings, when in 1930 the President of the College, the Secretary-General and the Executive Secretary, on his invitation, were the guests of the Fellows of the State at a luncheon during the meeting of the State Society at Pinehurst.

In Dr. McBrayer's death, his community, State and the country at large, have lost an enthusiastic, tireless worker in the field of preventive medicine.

C. H. Cocke, M.D.,
Governor for North Carolina.

DR. STEPHEN WEBB DAVIS

Dr. Stephen Webb Davis, of Charlotte, N. C., who died suddenly on March 16, 1938, was born September 1, 1894, the son of the late Thomas Jackson Davis and of Ella Webb Davis. Dr. Davis graduated from the Virginia Polytechnic Institute with a B.S. degree, and received the degree of M.D. from the University of Pennsylvania, with honors, in 1927. He served as Resident Physician at the University Hospital, in Philadelphia, and pursued postgraduate studies at the Mayo Clinic, the Government Research Station, at Beaufort, N. C., and other places. Prior to entering medicine, Dr. Davis served as First Lieutenant of the 11th Cavalry, U. S. Army, during the World War, being stationed in the West and on the Mexican border.

He was a member of Sigma Chi and Phi Chi (medical) fraternities, of the Mecklenburg County Medical Society, the North Carolina State Medical Society, the Tri State Medical Society of the Carolinas and Virginia, the Southern Medical Association, a Fellow of the American Medical Association, member of the American Heart Association, and became a Fellow of the American College of Physicians in 1936. He belonged to the Rotary Club of Charlotte, and to the Westmoreland Club of Richmond.

In June 1935, he married Miss Kate Jones, of Summerville, Ga., and leaves his wife and one daughter, born March 9, 1938.

Dr. Davis was largely interested in the progressive phases of Internal Medicine, developing, some years ago, an oxygen service, available to his colleagues, and lately was tremendously interested in peripheral vascular disease, equipping himself with all the modern instruments used in these conditions. He was an earnest student, an interested and zealous physician, and attempted to keep himself in the forefront of progress in his chosen field.

His sudden and unexpected death cut short what might well have been a very brilliant career in internal medicine.

C. H. Cocke, M.D.,
Governor for North Carolina.

MINUTES OF THE GENERAL BUSINESS MEETING

NEW YORK, N. Y., APRIL 7, 1938

The Annual Business Meeting of the American College of Physicians was held at the Waldorf-Astoria Hotel, New York City, April 7, 1938. The meeting was called to order at eleven-thirty o'clock by Dr. James H. Means, President.

Abstracted Minutes of the last Annual Business Meeting were read by the Executive Secretary, Mr. E. R. Loveland, which, upon motion duly seconded and carried, were accepted as read.

The Treasurer, Dr. William D. Stroud, reported that the finances of the College were in a satisfactory state, and that the accounts had been examined and found correct by a Certified Public Accountant. He reported that on December 31, 1937, the total assets of the College, according to book value, amounted to $205,383.47, of which $64,534.27 was in the Endowment Fund and $140,849.20 was in the General Fund; $63,308.98 represented the book value of investments in the Endowment Fund, the balance of the Fund being in cash. $64,941.60, according to book value, of the General Fund was invested in securities, the balance being represented partly in cash ($2,891.75), partly in the College Headquarters ($57,582.45), and partly in other assets as will be disclosed in the detailed financial reports following these Minutes. The Treasurer further referred to the detailed statements which hereafter follow.

Upon motion duly seconded and carried, the report of the Treasurer was accepted.

The Executive Secretary, Mr. E. R. Loveland, presented the following report:

"During the summer and early autumn of 1937, a completely new and revised Directory of the American College of Physicians was compiled and published. Under the direction and recommendations of the Board of Governors and the Board of Regents, the form of the Directory was somewhat changed, making it more informative and more practical.

"An extension of the activities of the College included the organization of Postgraduate Courses, restricted to members, given during the two weeks preceding the Annual Session. Although the project was started rather late and the final bulletins of the courses distributed only a month in advance of the Annual Session, there were formally registered 55 student-physicians in Course No. 1, in 'General Medicine,' at Harvard University Medical School; 27 student-physicians for Course No. 5, in 'General Medicine,' at the New York Post-Graduate Medical School and Hospital; 25 student-physicians for Course No. 6, 'Cardiovascular Diseases,' at the University of Pennsylvania Graduate School of Medicine; and 13 student-physicians for Course No. 7, 'Gastro-Intestinal Diseases,' also at the University of Pennsylvania Graduate School of Medicine.

"The Committee on Postgraduate Education, provided for by the Board of Regents, and appointed by the President, will continue its survey of graduate educational facilities in this country, and will also prepare a program of graduate courses for members of the College, the courses to be given in centers in or near-by the next meeting city. Full information will be published at the appropriate time in the ANNALS OF INTERNAL MEDICINE.

"The Twenty-Second Annual Session of the College in New York City has marked a high spot in the entire list of the Sessions of the College. The President, the General Chairman, the Vice Chairman and the local Committees have done a tremendous amount of work, and given the meeting much thought, which has resulted in a program second to none. The success of the meeting is attested to by the enthusiastic reports of our members and by the largest member regis-

tration at any Annual Session. The general registration was 2,228, with 319 visiting ladies, making a total of 2,547. The Round Table Conferences proved tremendously popular, with the result that we were unable to accommodate a great many of the members desiring tickets. No other innovation in the annual program has proved so popular.

"The attention of members is particularly called to the very high type of our Technical Exhibits this year, and that the number of exhibits has been reduced. The exhibits are being restricted to those having a direct relation to Internal Medicine and its allied specialties; many irrelevant and miscellaneous commercial exhibits have been eliminated. It is felt that exhibitors should be present primarily to give information and service, and not especially to make direct sales. The College desires to make its Commercial Exhibits scientific in character, and to enhance their value to its members. The revenue from exhibits goes a long way toward paying the expenses of the Annual Sessions; therefore, we owe the exhibitors our courteous attention. Members are urged to visit the various booths, for the exhibitors will be appreciative of the fact that the College members are sufficiently interested to examine the displays on which they have spent so much time and expense in preparation.

"The College accounts, according to our universal custom, have been audited by a Certified Public Accountant, and all the statements have been presented and approved by the Finance Committee and the Board of Regents. Through the coöperation of the Treasurer and the Secretary-General, and the help of a competent staff, the work in the Executive Offices of the College has been carried on with as great dispatch, promptness and efficiency as possible.

"In conclusion, I want to remind you again that we are always happy to have members visit us at our Headquarters in Philadelphia. We are gratified that so many have come during the past year, and any service we can perform is considered a privilege."

By motion duly seconded and carried, the report of the Executive Secretary was approved.

The Secretary-General, Dr. George Morris Piersol, presented the following report:

"The total membership of the American College of Physicians at this date is approximately as follows:

2	Masters
2,820	Fellows
1,080	Associates
3,902	Total

"During the past year, since our last Annual Session, 199 have been elected to Fellowship and 275 to Associateship. All but a very few of those elected to Fellowship were advanced from Associateship.

"Since the last Annual Session, we have lost through death, 58 members, consisting of 1 Master, 47 Fellows and 10 Associates.

"4 resignations of Fellows and 10 resignations of Associates, the latter due primarily to inability to qualify for Fellowship, have been accepted.

"All but about 7 per cent of those elected to Associateship five years ago qualified for Fellowship.

"The number who have taken advantage of Life Membership has been steadily growing. Since the last Annual Session, 22 have subscribed to Life

Membership, making a grand total of 101. However, due to deaths of 4 Life Members, there remain 97. The names of the Life Members of the College are not only entered in the Directory of the College, but their names appear on the Life Membership Scroll, which is exhibited in the College Booth, space No. 36, in the Exhibit Room."

Upon motion duly seconded and carried, the report of the Secretary-General was accepted.

On behalf of the Board of Regents, in consideration of his services as President of the College, the Secretary-General, Dr. Piersol, presented to the outgoing President of the American College of Physicians, Dr. James H. Means, a silver, engraved, ferruled Gavel. Dr. Means accepted the Gavel and expressed his deep appreciation therefor.

At this point, Dr. Means called upon the incoming President, Dr. William J. Kerr, to take over the chairmanship of the meeting.

Dr. Kerr, in taking the chair, addressed the College as follows:

"I feel very humble in standing before you today to accept this high office in the College. It is a little more than a year ago when I began to receive some letters from friends congratulating me upon my election, or selection for the Presidency of the College. I had not seen notice in the ANNALS. That was the first intimation that any such honor could ever come my way. I must say that I was greatly surprised and I still don't understand.

"During this year of preparation for the job which lies ahead, I have felt a good deal of temerity in assuming the position, and when I have thought of the very distinguished men who have preceded me in this position and noted their accomplishments, I had hoped that I might be able to rise to the occasion.

"If you do not mind some references which I may now make, and not in a facetious mood, because this is a very serious moment in my life, I would like to liken the College to a certain long-necked bird, a land bird, if you will, one which goes rather steadily in a forward direction but with a long neck and head on the end which may be represented by your President, moving about a little here and there from side to side and up and down, but still the old bird moving steadily forward.

"This is a ground bird and the wings are not developed for flight. The chief organ of this bird is the gizzard, which accepts all manner of things which are provided and brought before it, and this is represented by our honorable Board of Regents and Governors who have to pass upon many and sundry things presented, and I must say through my brief experience on this Board that I never saw a group of men who could master problems in a more efficient manner.

"The plumage of this bird is represented by the Fellows and Associates of the College who can be recognized throughout the length and breadth of our land, including Canada and other countries near-by, because of their outstanding accomplishments which everyone in the community can well recognize.

"The chief means of defense of this particular bird is the long leg with strong toes which is provided only for a frontal attack. This bird cannot kick backwards, but only by a frontal attack can it meet its enemies and meet the problems which arise, and we are, I think, hoping that in the College we may be able to continue to anticipate danger ahead or problems ahead and meet them squarely when they come.

"Through the great speed of this bird, it has not been necessary to prepare defenses toward the rear. I may say, so far as I can understand the position of the College in the country today, we are rapidly outstripping all of our competitors.

"By now, I think you will recognize that this bird is a male, and since it is the custom among this species for the male to sit on the nest and hatch the eggs, in our College there have been several notable hatchings, chief among them now classed as our living offspring are the ANNALS OF INTERNAL MEDICINE, the College home with its very efficient staff presided over by Mr. Loveland, the American Board of Internal Medicine, not yet full grown but developing well and rapidly, for the certification of internists in this country, then our educational features, chief among which during the past many years have been our Annual Sessions, and more recently the regional meetings throughout the country.

"During the last year, we have added the postgraduate effort in the College and from the response which we had this year, even though we had a late start, we are encouraged to believe that this may prove to be one of the most successful and helpful of our endeavors for the membership in the College. It shows an abiding interest in keeping up that which has always distinguished the members of the profession in our special field.

"We are hoping during the next year to increase our activities in this direction and perhaps to make some surveys in coöperation with other agencies on the possibilities for postgraduate instruction in this country.

"It is hoped, in returning to the bird, that your President as the temporary and roaming head of this great organism may be able to keep his head out of the sand. He is a little beyond the place of the shifting sands in this country today, but it is to be hoped that he will keep awake to situations arising in the country.

"If I can bring to the College the spirit of our last and rapidly diminishing frontier in the West, I shall be very happy. If the impressive water falls, the giant peaks and trees of the West have any influence upon land, then I hope that I may be able to translate some of it into activity upon behalf of the College as a whole.

"There are two things which are very close to my heart in relation to the College. One of them is the matter of postgraduate training upon which we have already embarked, but in a very small way. There is another matter with respect to the dues. We hope that after due deliberation we may find some way to reduce the annual dues for members in the College. It may not be much, but we hope that it may be able to be accomplished.

"In concluding these remarks, I wish to assure you that I shall labor diligently for the whole College, and I hope that I shall not let you down during my year in office. Thank you!"

Upon motion duly seconded and carried, it was

Resolved, that in accordance with the present By-Laws of the American College of Physicians and directions of the Board of Regents at a regular meeting held on April 18, 1937, and in accordance with the publication of such proposed amendment to the members in accordance with the present By-Laws, an addition shall be made to the By-Laws, Article IV, Section 1, as an additional paragraph, as follows:

"Any member of the Board of Governors unable to attend the Annual Session shall appoint as his alternate, with all the privileges of a Governor, a Master or Fellow of his district who will be in attendance at that Session. Upon presentation to the Chairman of the Board of Governors of a certificate of appointment, the alternate shall be recognized and act in the full capacity of Governor for the Session to which he has been appointed. The same alternate shall not be appointed for more than two consecutive years."

President Kerr then called for a report of the Committee on Nominations by the Chairman, Dr. Jonathan C. Meakins, whose report herewith follows:

"Mr. President:

I beg to report on behalf of the Nominating Committee.

In accordance with the By-Laws, Article I, Section 2, we submit the following names:

(*A*) *For the Elective Offices:*

President-Elect ..... O. H. Perry Pepper, Philadelphia, Pa.
First Vice-President ..... James B. Herrick, Chicago, Ill.
Second Vice-President ..... Noble Wiley Jones, Portland, Ore.
Third Vice-President ..... Charles T. Stone, Galveston, Tex.

This list of nominees has been duly published in the ANNALS OF INTERNAL MEDICINE at least one month before the present date.

(*B*) *For the Board of Regents:*

For the Term Expiring 1940

David P. Barr, St. Louis, Mo.

For the Term Expiring 1941

James E. Paullin, Atlanta, Ga.
Robert A. Cooke, New York, N. Y.
Hugh J. Morgan, Nashville, Tenn.
Ernest E. Irons, Chicago, Ill.
D. Sclater Lewis, Montreal, Que.

(*C*) *For the Board of Governors:*

For the Term Expiring 1940

Eugene H. Drake ..... MAINE—Portland
M. D. Levy ..... TEXAS—Houston

For the Term Expiring 1941

James F. Churchill ..... SOUTHERN CALIFORNIA—San Diego
James Waring ..... COLORADO—Denver
Francis G. Blake ..... CONNECTICUT—New Haven
Wallace M. Yater ..... DISTRICT OF COLUMBIA—Washington
Samuel E. Munson ..... SOUTHERN ILLINOIS—Springfield
Robert M. Moore ..... INDIANA—Indianapolis
Thomas Tallman Holt ..... KANSAS—Wichita
William B. Breed ..... MASSACHUSETTS—Boston
Warren Thompson ..... NEBRASKA—Omaha
Leander A. Riely ..... OKLAHOMA—Oklahoma City
Nelson G. Russell ..... WESTERN NEW YORK—Buffalo
R. R. Snowden ..... WESTERN PENNSYLVANIA—Pittsburgh
Edward L. Bortz ..... EASTERN PENNSYLVANIA—Philadelphia
John L. Calene ..... SOUTH DAKOTA—Aberdeen
J. Owsley Manier ..... TENNESSEE—Nashville
Louis E. Viko ..... UTAH—Salt Lake City
Harry L. Arnold ..... HAWAII—Honolulu
J. H. Holbrook ..... ONTARIO—Hamilton, Canada
C. F. Moffatt ..... QUEBEC—Montreal, Canada
William M. James ..... PANAMA and the CANAL ZONE"

President Kerr then asked if there were other nominations to be made from the floor. There were none, and upon motion duly seconded and unanimously carried, it was

Resolved, that the nominations be closed and that the secretary cast the ballot for the election of the nominees presented by the Nominating Committee.

President Kerr then asked for the presentation of other business, whereupon the following resolution, offered by Dr. Jonathan C. Meakins, was duly seconded and unanimously carried with a rising vote:

Resolved, that the cordial thanks of the American College of Physicians be extended to the Retiring President, Dr. James H. Means; to the General Chairman, Dr. James Alex. Miller; and to the Vice Chairman and members of his various committees, individually and collectively, for their faithful work in the preparation and conduct of the New York Session; to the Ladies Entertainment Committee for their efficiency and courteous entertainment of our visiting ladies; to the medical schools and hospitals of New York City for putting their facilities at the disposal of the College, and for their helpful participation; to the New York Convention Bureau and its Director for their assistance; and the Waldorf-Astoria Hotel and its Convention Manager for their coöperation.

Adjournment.

Executive Secretary's Report

1937

The auditor's report of his examination of the accounts of the College is hereto attached. Even with added activities affecting the finances of the College, such as the gift of one thousand dollars to the National Conference on Nomenclature of Diseases and the writing off of one thousand dollars as depreciation on the Headquarters Building, as directed by the Board of Regents, the surplus is still favorable as below indicated:

1935	Surplus	$ 17,182.09
1936	"	24,946.53
1937	"	23,765.75

The 1937 surplus was distributed as follows:

Endowment Fund	$ 2,749.45
General Fund	21,016.30
	$ 23,765.75

The total principals of the two Funds on December 31, 1937, were

Endowment Fund	$ 64,534.27
General Fund	140,849.20
	$205,383.47

For comparison, the total assets of the College in 1926 were only $9,000.00. The growth of the activities and services of the College has been greatly expanded during the intervening years, yet there has been built up an excellent financial foundation. Conservative policies and aggressive effort are responsible, although the general momentum and natural growth have contributed much in recent years. The

journal, ANNALS OF INTERNAL MEDICINE, was for many years the source of considerable deficits. Volume I showed but ten and three-quarters pages of paid advertising; Volume X (completed, June 1937) showed two hundred and sixty-seven pages of paid advertising. Volume I had an average circulation of 1803; Volume X, 3878. The March, 1938, issue (Vol. XI, No. 9) had a circulation of 4210. But the College has also given its members more as the journal grew; Volume I had 1040 pages of scientific content; Volume X, 1786 pages.

During 1937 a new and revised Directory of the College was published in accordance with recommendations of the Board of Governors and the Board of Regents. The Directory contains 621 pages, and was published at a total cost, including cost of distribution, of slightly over $4,000.00. The cost in labor and funds is well justified by its wide use by members of the College, medical societies, medical schools, hospitals, insurance companies and other agencies.

The budgets for 1938 were approved in detail by the Board of Regents December 12, 1937.

Respectfully submitted,

(Signed) E. R. LOVELAND,
Executive Secretary

January 1, 1938.

H. I. MACLEAN

309 Valley Road

Llanerch, Pa.

March 4, 1938

To the Board of Regents

American College of Physicians, Inc.
Philadelphia, Pa.

Mr. E. R. Loveland, Executive Secretary

Dear Sirs:

I have examined the accounts of the

AMERICAN COLLEGE OF PHYSICIANS, INC.

for the year ended December 31, 1937, and the accompanying statements, including the Balance Sheet at December 31, 1937, the analyses of the General Fund and the Endowment Fund, and the Detailed Statement of Operations for the year ended December 31, 1937, are in accordance with the books of account and in my opinion set forth correctly the financial position at December 31, 1937, and the results of operations for the calendar year ended December 31, 1937, subject to the following comments:

Cash: The cash was properly accounted for. The following is a statement of the cash in the various depositories:

Girard Trust Company, Philadelphia	$2,313.75
Provident Trust Company, Philadelphia	861.47
Royal Bank of Canada, Montreal	741.82
	$3,917.04

The amount of cash in closed banks at January 1, 1937, was $6,292.39; during the year a liquidating dividend amounting to $583.06 was received, which reduced the amount to $5,709.33, as shown by the following schedule:

	Balance Jan. 1, 1937	*Liquidating Dividend*	*Balance Dec. 31, 1937*
Bank of Pittsburgh, Pittsburgh	$1,461.97		$1,461.97
Exchange National Bank, Pittsburgh	1,749.20	$583.06	1,166.14
Highland National Bank, Pittsburgh	3,081.22		3,081.22
	$6,292.39	$583.06	$5,709.33

Accounts Receivable: The accounts receivable were examined and found to be less than one year old and appear to be good and collectible. The detailed accounts receivable were in agreement with the control account. No requests for confirmation of the accounts were mailed.

Investments: The securities were accounted for by direct correspondence and the income for the period under review was verified.

General: The increase in the amount of the Endowment Fund and the General Fund during the year 1937 is as follows:

	Balance Jan. 1, 1937	*Net Increase*	*Balance Dec. 31, 1937*
Endowment Fund	$ 61,784.82	$ 2,749.45	$ 64,534.27
General Fund	119,832.90	21,016.30	140,849.20
	$181,617.72	$23,765.75	$205,383.47

In accordance with the instructions of the Executive Secretary, the prepaid insurance at December 31, 1937, was not set up as a deferred expense; the other deferred and accrued items were verified; the charges to the College Headquarters account were examined, and in my opinion appear to be proper charges to this account; the charges to the Furniture and Equipment accounts represent proper additions to this account and the allowance for depreciation appears to be adequate; a depreciation reserve account has been set up for the new building in accordance with the action of the Board of Regents at the meeting on December 12, 1937, which provided that depreciation on the building should be taken into account at the rate of $1,000.00 per year; the footings and extensions of the inventory were verified; all ascertainable liabilities have been included in the balance sheet; all recorded receipts from dues, initiation fees, exhibits, advertising, sales of publications, etc., were properly deposited in bank and all disbursements, as indicated by the vouchers, cancelled checks and bank statements, were properly recorded in the books of account.

Very truly yours,

(Signed) H. I. MacLEAN,
Certified Public Accountant

AMERICAN COLLEGE OF PHYSICIANS, INC.

Balance Sheet, December 31, 1937

General Fund

Assets			*Liabilities*	
Cash in banks and on hand		$ 2,891.75	Accounts Payable	$ 22.50
Accounts Receivable:			Deferred Income:	
Advertising	$ 749.78		Advance Subscriptions for Volumes XII and XIII, ANNALS OF INTERNAL MEDICINE	443.81
Kenyon and Eckhardt, Inc.	169.00	918.78		
Inventory of Keys, Pledges and Frames, at cost		349.55		
Accrued Income on General Fund Investments		564.37		
Accrued Income on Endowment Fund Investments Due to General Fund		659.36		
Investments at Book Value		64,941.60		
Insurance Deposit		555.00		
Deferred Expenses, 22nd Annual Session		2,563.56		
Deferred Claims:				
Banks in process of liquidation:				
Bank of Pittsburgh	$ 1,461.97			
Exchange National Bank, Pittsburgh	1,166.14			
Highland National Bank, Pittsburgh	3,081.22	5,709.33	General Fund, as annexed	140,849.20
College Headquarters, Real Estate	57,582.45			
Less, Allowance for Depreciation	1,000.00	56,582.45		
Furniture and Equipment, at cost	9,247.23			
Less, Allowance for Depreciation	3,667.47	5,579.76		
		$141,315.51		$141,315.51

Endowment Fund

Cash in banks	$ 1,225.29	Endowment Fund, Principal	$ 64,534.27
Accrued Interest	659.36	Accrued Income Due General Fund	659.36
Investments at Book Value	63,308.98		
	$ 65,193.63		$ 65,193.63
TOTAL ASSETS	$206,509.14	TOTAL LIABILITIES AND FUNDS	$206,509.14

GENERAL FUND

For the Year Ended December 31, 1937

Balance, January 1, 1937			$119,832.90
Less:			
Transfer to Endowment Fund of the Initiation Fees of Life Members			730.00
			$119,102.90
Summary of Operations for the Year ended December 31, 1937:			
Income:			
Annual Dues		$24,695.08	
Subscriptions, ANNALS OF INTERNAL MEDICINE		24,649.79	
Advertising, ANNALS OF INTERNAL MEDICINE		8,863.51	
Initiation Fees		11,616.50	
Income from Invested Funds (General)		2,164.16	
Exhibits, 21st Annual Session		9,832.66	
Guest Fees, 21st Annual Session		421.00	
Other Income		351.26	
Profit on Investments of General Fund sold (net)		1,420.51	$84,014.47
Expenses:			
Salaries		$19,533.78	
Postage, Telephone, Telegraph		3,399.04	
Office Supplies and Stationery		1,054.76	
Printing		19,562.84	
Traveling Expenses		4,342.72	
College Headquarters:			
Maintenance	$2,109.16		
Taxes	1,253.07		
Insurance	86.77		
Miscellaneous	100.00	3,549.00	
Depreciation on Building, Furniture and Equipment		1,847.02	
Grant to the National Conference on Nomenclature of Diseases		1,000.00	
Printing 1937 Directory		4,039.31	
Other Expenses:			
21st Annual Session	2,260.49		
ANNALS OF INTERNAL MEDICINE	257.51		
Miscellaneous	1,421.70	3,939.70	62,268.17
Net Income for the Year Ended December 31, 1937			21,746.30
Balance, December 31, 1937			$140,849.20

ENDOWMENT FUND

For the Year Ended December 31, 1937

Principal Account, January 1, 1937			$61,784.82
Add:			
Life Membership Fees received during 1937		$2,270.00	
Transfer of Initiation Fees of New Life Members from General Fund		730.00	3,000.00
			$64,784.82
Deduct:			
Loss on Sale of Investments			250.55
Principal Account, December 31, 1937			$64,534.27
*Income Account:			
Income from Investments earned during 1937			$ 2,428.54
Deduct:			
Research Fellowships		$2,330.25*	
John Phillips Memorial Prize		98.29	2,428.54

* $69.75 additional was expended from the General Fund during 1937 on account of the Research Fellowships.

Detailed Statement of Operations

For the Year Ended December 31, 1937

General Income:

Annual Dues		$24,695.08	
Initiation Fees		11,616.50	
Income from General Fund Investments		2,164.16	
Profit from Sales of Keys, Pledges and Frames		181.94	
Profit on Investments of General Fund sold (net)		1,420.51	
Dividend on Insurance Deposit		60.00	$40,138.19

Twenty-first Annual Session:

Expenses:			
Salaries		$ 4,049.99	
Communications (Postage, Telephone, etc.)		480.17	
Office Supplies and Stationery		144.65	
Printing		1,061.11	
Traveling Expenses		2,418.32	
Other Items:			
Advertising	$ 100.70		
Badges	191.50		
Convocation	492.59		
Ladies Committee	502.81		
Reporting	90.00		
Smoker	342.27		
Other Miscellaneous Items	540.62	2,260.49	10,414.73
Income:			
Exhibits (Net)		$ 9,832.66	
Guest Fees		421.00	
Profit on Banquet		109.32	10,362.98
Net Expenses of Annual Session			51.75

Annals of Internal Medicine:

Income:			
Subscriptions:			
Volume I	$ 14.27		
Volume II	10.49		
Volume III	9.02		
Volume IV	9.62		
Volume V	7.63		
Volume VI	12.68		
Volume VII	28.75		
Volume VIII	31.45		
Volume IX	90.07		
Volume X	1,369.22		
Volume XI	23,066.59	$24,649.79	
Advertising (Net):			
Volume X	$ 4,243.94		
Volume XI	4,619.57	8,863.51	
		$33,513.30	
Expenses:			
Salaries	$ 6,310.74		
Communications (Postage, Telephone, etc.)	1,195.03		
Office Supplies and Stationery	303.89		
Printing	17,443.92		
Miscellaneous	156.88		
Allowances, Adjustments and Purchases	100.63	25,511.09	
Net Profit on Annals of Internal Medicine			8,002.21
Total Income			$48,140.40

Executive Secretary's Office:			
Expenses:			
Salaries	$ 9,173.05		
Communications (Postage, Telephone, etc.)	1,723.84		
Office Supplies and Stationery	606.22		
Printing	1,057.81		
Maintenance	32.73		
Traveling Expenses	1,924.40		
Fee to Custodian of Securities	151.13		
Miscellaneous Items	494.09	15,163.27	
College Headquarters:			
Maintenance	$ 2,109.16		
Taxes	1,253.07		
Insurance	86.77		
Miscellaneous	100.00	3,549.00	
Other Expenses:			
Investment Counsel Service		200.00	
ANNALS OF INTERNAL MEDICINE Distributed Free to Life Members		474.00	
Printing 1937 Directory, net		4,039.31	
Grant to the National Conference on Nomenclature of Disease		1,000.00	
Research Fellowships (amount not provided by Income of Endowment Fund)		69.75	
Depreciation:			
Building	$ 1,000.00		
Furniture and Equipment	847.02	1,847.02	26,394.10
Net Income for the Year Ended Dec. 31, 1937			$21,746.30

INVESTMENTS

December 31, 1937

Par Value	*Bonds*	*Endowment Fund Securities*	*General Fund Securities*
$ 5,000	Bell Telephone of Canada, 5s, 1955	$ 5,562.50	
2,000	Canadian National (West Indies) SS. Co., Ltd., 5s, 1955	2,040.00	
5,000	Cities Service Co., 5s, 1950		$ 4,075.90
1,000	City of Montreal, 5s, 1956	1,071.30	
5,000	Columbia Gas and Electric Corp., Deb., 5s, 1961		4,956.25
5,000	Commonwealth Edison Co., First, Series "F," 4s, 1981	4,744.35	
5,000	Government of the Dominion of Canada, 4s, 1960	4,662.50	
2,000	Great Northern Railway Co., Series "H," 4s, 1946	2,100.45	
3,000	Great Northern Railway Co., Series "H," 4s, 1946		2,910.45
5,000	New York Central RR., 3¾s, 1946	4,900.00	
1,000	North American Edison Co., Deb., Series "A," 5s, 1957		1,007.75
5,000	Northern States Power Co., 1st & Ref. Mort., 3½s, 1967	4,806.25	
2,000	Ohio Edison Co., 1st Mort., 4s, 1965	2,115.00	
3,000	Ohio Edison Co., 1st Mort., 4s, 1965		3,172.50
5,000	Pennsylvania Railroad, Gen., 4¼s, Series "E," 1984		5,013.10
2,000	Port of New York Authority, New York-New Jersey Interstate Bridge, 4½s, Series "B," 1952	2,042.20	
2,000	Port of New York Authority, New York-New Jersey Interstate Tunnel, 4¼s, Series "E," 1958	2,065.40	

5,000	Southern Kraft Corp., 1st Leasehold & Gen. Mort., 4¼s, 1946		5,062.50	
5,000	Southern Pacific Co., 3¾s, 1946		5,008.65	
5,000	Texas and Pacific Railway, Gen. and Ref., B, 5s, 1977	5,313.40		
2,000	U. S. Treasury, 4s, 1954	1,998.13		
20,000	U. S. Treasury, 3¼s, 1945	19,887.50		
5,000	Virginia Public Service, 5½s, 1946		5,133.65	
$100,000	TOTALS, Bonds	$63,308.98	$36,340.75	$ 99,649.73
Shares	*Stocks*			
50	Atchison, Topeka and Santa Fe		$ 4,970.75	
30	Caterpillar Tractor Co.		3,014.40	
50	Chase National Bank of New York		2,775.00	
50	Continental Can Co., Inc.		5,125.00	
150	Pacific Gas & Electric Corp.		4,640.50	
20	J. C. Penny Co.		1,375.30	
50	Timken Roller Bearing Company		3,407.25	
50	Union Carbide & Carbon Corporation		3,292.65	
	TOTAL, Stocks		$28,600.85	
	TOTAL, Investments	$63,308.98	$64,941.60	$128,250.58

REPORT ON REGISTRATION OF THE TWENTY-SECOND ANNUAL SESSION OF THE AMERICAN COLLEGE OF PHYSICIANS

New York, N. Y. April 4–8, 1938

Below appears a distribution of the registration at the New York Session of the College. The member attendance was the highest at any meeting in the history of the College. The guest attendance was restricted very largely to guest clinicians and speakers, since the physical facilities could not accommodate the large number of guests that would attend if admission were open to all members of the local county medical societies in the district.

The New York registration compares with previous registrations as follows:

Session	*Members*	*Guest Physicians*	*Students*	*Exhibitors*	*Guest Non-Physicians*	*Visiting Ladies*	*Total*
NEW YORK (1938)	1447	463	3	291	24	319	2,547
ST. LOUIS (1937)	877	589	414	201	30	210	2,321
DETROIT (1936)	733	539	172	132		103	1,679
PHILADELPHIA (1935)	923	749	346	231		195	2,444
CHICAGO (1934)	690	660	420	194		121	2,085

REGISTRATION BY STATES

Provinces and States	*Members*	*Guests*	*Total*
UNITED STATES			
ALABAMA	9		9
ARIZONA	4		4
ARKANSAS	5	1	6
CALIFORNIA	26	2	28
COLORADO	11	1	12
CONNECTICUT	54	6	60
DELAWARE	7	1	8
DISTRICT OF COLUMBIA	33	3	36
FLORIDA	13		13
GEORGIA	18	1	19
IDAHO	1		1
ILLINOIS	37	12	49
INDIANA	13	2	15
IOWA	9		9
KANSAS	10		10
KENTUCKY	10	2	12
LOUISIANA	13	1	14
MAINE	12	1	13
MARYLAND	48	4	52
MASSACHUSETTS	70	18	88
MICHIGAN	60	6	66
MINNESOTA	25	8	33
MISSISSIPPI	7		7
MISSOURI	16	1	17
MONTANA	5		5
NEBRASKA	10	1	11
NEW HAMPSHIRE	5	2	7
NEW JERSEY	74	7	81
NEW MEXICO	1		1
NEW YORK	375	293	668
NORTH CAROLINA	30	3	33
NORTH DAKOTA	2		2
OHIO	77	16	93
OKLAHOMA	11	2	13
OREGON	6	3	9
PENNSYLVANIA	163	30	193
RHODE ISLAND	16	2	18
SOUTH CAROLINA	7	3	10
SOUTH DAKOTA	2		2
TENNESSEE	10		10
TEXAS	18	1	19
UTAH	3	1	4
VERMONT	3	2	5
VIRGINIA	36	1	37
WASHINGTON	5	1	6
WEST VIRGINIA	22	4	26
WISCONSIN	11	4	15
CANAL ZONE			
ANCON	1		1

Provinces and States	*Members*	*Guests*	*Total*
PHILIPPINE ISLANDS			
MANILA		1	1
PUERTO RICO			
SAN JUAN	2		2
FOREIGN			
CANADA			
ALBERTA	1		1
BRITISH COLUMBIA	1	1	2
MANITOBA	1		1
NEW BRUNSWICK	5	1	6
NOVA SCOTIA	1		1
ONTARIO	18	11	29
QUEBEC	12	1	13
SASKATCHEWAN	1		1
FINLAND			
HELSINGFORS		1	1
HUNGARY			
BUDAPEST		1	1
REPUBLIC OF PANAMA			
PANAMA	1		1
Total	1,447	463	1,910
Total Visiting Ladies			319
Total Students			3
Total Exhibitors			291
Total Guest Non-Physicians			24
GRAND TOTAL			2,547